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THE SYNTHETIC UTILITY OF OXYALLYL CATIONS

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1. INTRODUCTION

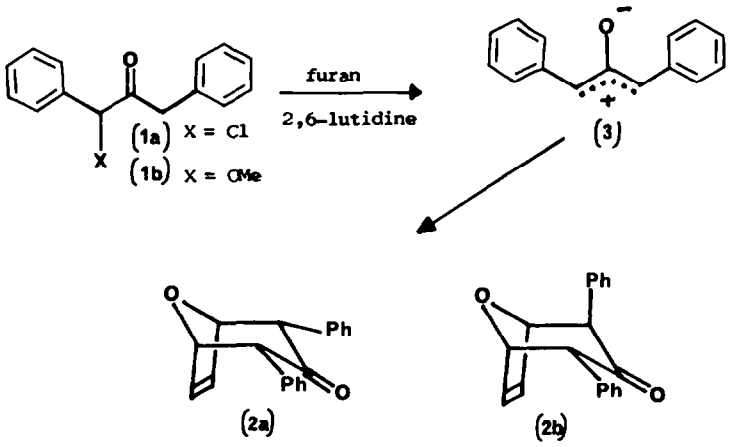
It is now 13 years since Hoffmann first reviewed[1] the chemistry of oxyallyl cations; and more recently, both he and Noyori—the other pioneer of oxyallyl chemistry—have produced extensive, updated reviews of the subject.[2,3] The purpose of this report is to assess the practical utility of oxyallyl cations, by considering instances where they have participated as key intermediates in syntheses of natural products and related structures. No attempt will be made to give an exhaustive account of the plethora of novel structures that may be made (often in low yield) using oxyallyls, since Noyori has provided an extensive tabular survey of all such reaction products.[3] Mechanistic considerations will also be largely omitted since these are discussed in detail by Hoffmann.[2] The emphasis will be on synthetic utility.

2. PREPARATION OF OXYALLYL CATIONS

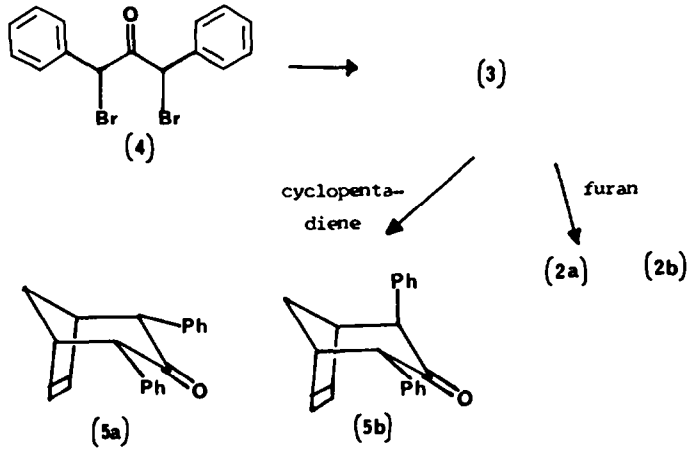
2.1. *Reduction of* α,α′-dihaloketones

Oxyallyl cations were first generated, probably unwittingly, by Fort[4] when he treated α-chlorodibenzyl ketone (**1a**) with 2,6-lutidine in the presence of furan (DMF, 4 days at 25°), and obtained cycloadduct **2a** (Scheme 1). A related experiment[5] in which methanol was used as solvent yielded the α-methoxy ketone (**1b**), thus providing evidence for the intermediacy of the oxyallyl cation (**3**).† Improved methods for the production of **3** were introduced by Cookson *et al.* who treated α,α′-dibromoketone (**4**) with sodium iodide, zinc–copper couple, or with mercury in order to generate

† Oxyallyl cations are, of course, acyclic mesomeric betaines, and the reader is referred to the seminal accounts by Huisgen (*Angew. Chem.* **2**, 565 (1963)) and Ollis (*Tetrahedron* **41**, 2239 (1985)) for excellent reviews of the whole subject of mesomeric betaines.



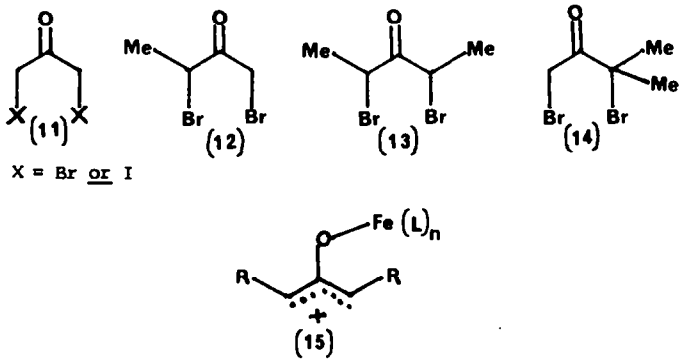
Scheme 1.

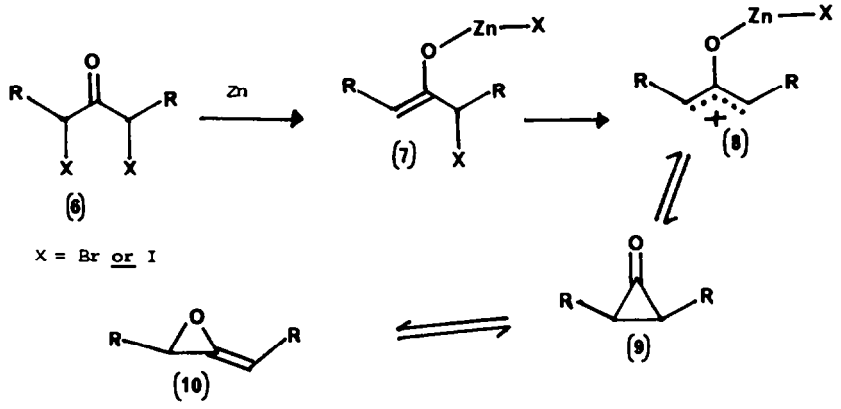


Scheme 2.

oxyallyl **3**, and thence obtain cycloadducts **2a** and **b** through reaction with furan, and **5a** and **b** upon reaction with cyclopentadiene (Scheme 2).

Hoffmann and co-workers subsequently studied[7,8] the feasibility of generating oxyallyl cations from a variety of simple α,α′-dihaloketones and in this way established the minimum structural requirements necessary for the formation of viable oxyallyl cation intermediates. Typically a two-electron reduction of dihaloketone (**6**) was accomplished using zinc, and the resultant metal enolate (**7**) then suffered an S_N1-type ionization (probably facilitated by the zinc dihalide formed), with loss of the allylic halogen and formation of the oxyallyl cation (**8**) in the form of its metal enolate (Scheme 3).



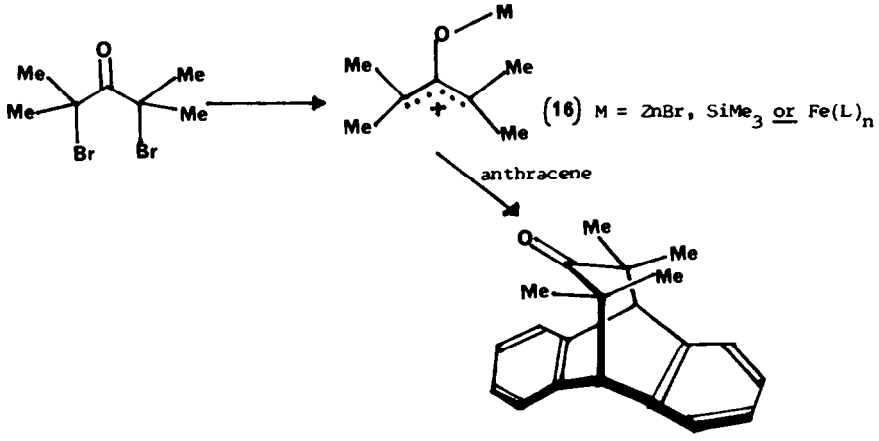


Scheme 3.

Two structural isomers are considered to be in equilibrium with **8**, namely cyclopropanone (**9**) and allene oxide (**10**). The oxyallyl species (**8**), in a free dipolar form is very labile, and is believed to isomerize immediately to **9** and **10**,[9,10] unless trapped by a suitable diene or solvent. It can, however, be stabilized by electron-releasing substituents (i.e. inductive or mesomeric effects) (R = alkyl, aryl, or halo), and by an increase in the covalent character of the metal–oxygen bond. Thus Hoffmann found that oxyallyl cations from α,α′-dihaloacetones (**11**), or from 1,3-dibromobutanone (**12**) were too labile to be trapped by dienes, whilst 2,4-dibromopentan-3-one (**13**) and 1,3-dibromo-3-methylbutan-2-one (**14**) served as effective precursors of the corresponding oxyallyls.

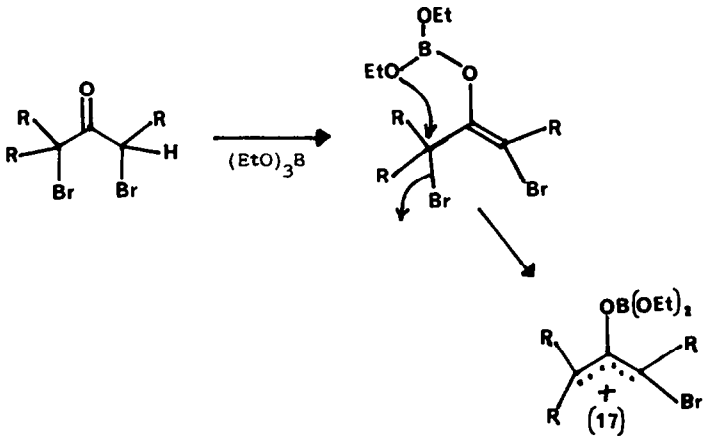
At about the same time Noyori *et al.* demonstrated the efficacy of a system involving diiron enneacarbonyl (Fe_2CO_9) in conjunction with α,α′-dibromoketones,[11] presumably with obtention of the oxyallyl cation (**15**), which has a highly covalent iron–oxygen bond. A similar kind of iron enolate can be obtained using iron–graphite (prepared from ferric chloride and potassium graphite) and α,α′-dibromoketones.[12]

These two reductive methods have been refined over the years, and the majority of recorded reactions of oxyallyls have employed species like **8** and **15**. The zinc enolate (**8**) is less electrophilic than the corresponding iron enolate (**15**), due to greater covalency of the metal–oxygen bond in the latter species; and in consequence, cycloaddition reactions with poorly nucleophilic dienes proceed best with diiron enneacarbonyl as reductant. The reaction illustrated in Scheme 4 is exemplary[13] and employs oxyallyls from 2,4-dibromo-2,4-dimethylpentan-3-one (**16**).



M	Yield (%)
ZnBr	3
$SiMe_3$	71
$Fe(L)_n$	90

Scheme 4.



Scheme 5.

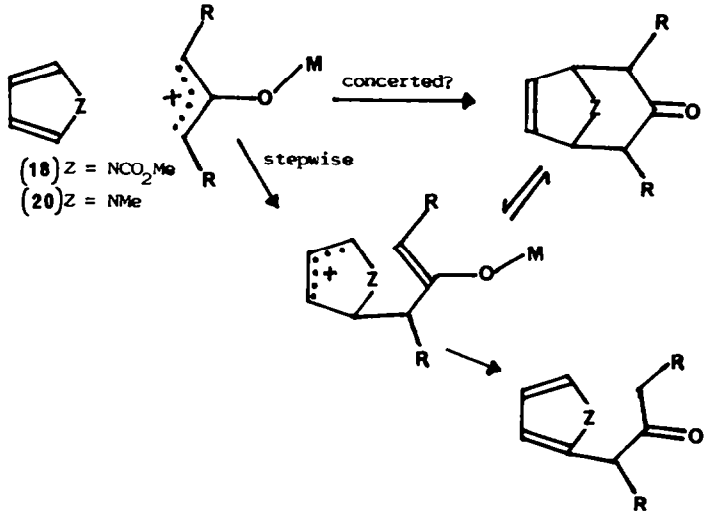
The trimethylsiloxy- species (**16**, M = $SiMe_3$), which can be prepared by using chlorotrimethylsilane in conjunction with a zinc–copper couple,[14] is of intermediate electrophilic character, and the yields of cycloadducts are better than those obtained with zinc enolates.

Boron enolates (**17**) are formed when triethylborate and polybromoketones are employed, and the mechanism shown in Scheme 5 has been proposed[15] to account for the formation of **17**. Since an initial proton loss is involved, tetraalkylated dibromoketones cannot be employed.

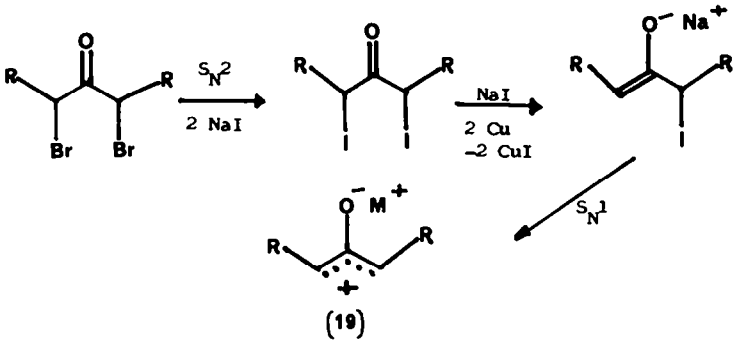
When electron-rich dienes like pyrroles are required to react with oxyallyl cations, zinc oxyallyls and iron oxyallyls cannot be employed, since fragmentation of the cycloadduct occurs to yield alkylated pyrroles[16,17] (Scheme 6). This fragmentation can be controlled by reducing the electron density on the pyrrole nitrogen atom, e.g. by employing N-carbomethoxypyrrole (**18**).[18] The mechanisms suggested in the scheme will be discussed later.

A better method is to employ iodide (from sodium iodide) as reducing agent, with copper powder present to scavenge the molecular iodine formed. Here a sodium oxyallyl (**19**, M = Na) is formed, and the mechanism shown in Scheme 7 has been established[19] for its production. Using this reagent good yields of cycloadducts may be obtained with simple alkyl pyrroles,[17,20] e.g. with N-methylpyrrole (**20**) (Scheme 6).

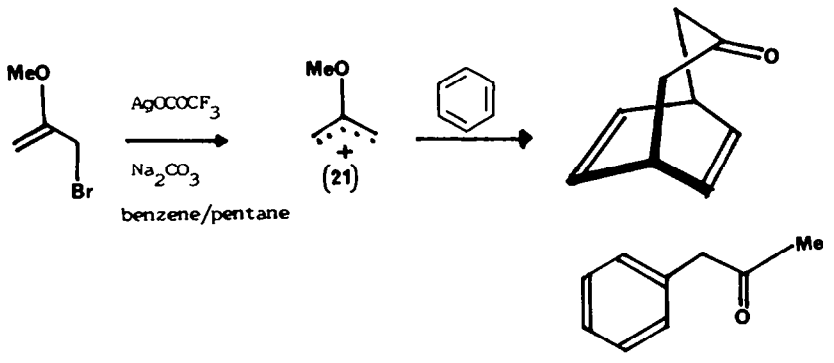
Use of lithium iodide in place of sodium iodide produces a lithium oxyallyl (**19**, M = Li), and this is more electrophilic than the corresponding sodium oxyallyl, yielding mainly alkylated pyrroles in cycloadditions with electron-rich pyrroles.



Scheme 6.



Scheme 7.



Scheme 8.

A summary of the main features of the various reductive methods, including their advantages and disadvantages, is given in Table 1.

2.2. *Reaction of α-haloketones with bases*

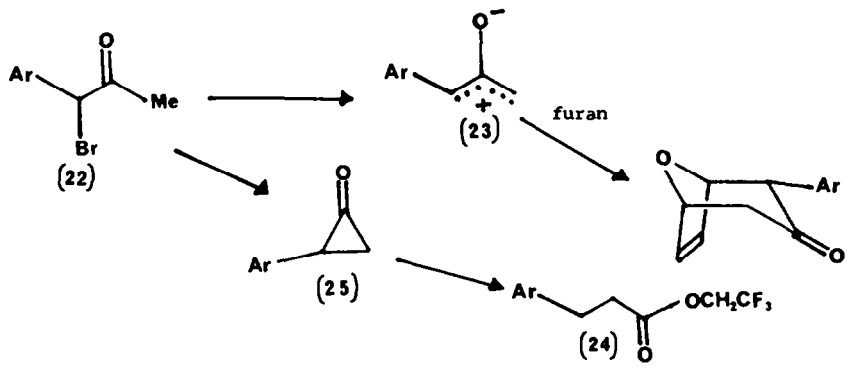
In this general category, we can include the original experiments of Fort[4] involving the treatment of an α-bromoketone with base (Scheme 1), and the pioneering work of Hoffmann and co-workers[21,22] on the generation of the 2-methoxyallyl cation (**21**) from 2-methoxyallyl bromide and silver trifluoroacetate (Scheme 8).

The former method has been extended by Mann and co-workers,[23,24] who showed that simple α-bromobenzyl, alkyl ketones (**22**) can be converted into the corresponding oxyallyl cations (**23**), and that these can be trapped by furans (Scheme 9). The reactions proceed well in methanol with triethylamine as base, and even better if 2,2,2-trifluoroethanol is used as solvent. Variable amounts of the trifluoroethyl esters (**24**) are produced[24] when this latter solvent is employed, and these probably arise via the intermediacy of cyclopropanone (**25**).

When the aryl group is electron rich (e.g. di- or trimethoxyphenyl) the intermediate oxyallyl

Table 1

Method	Typical conditions	Comments
Fe_2CO_9 and related iron species	benzene, room temp to 60°, 2–48 h	works with most α,α′-dibromoketones, produces the most electrophilic oxyallyl cation
Zn–Cu and Zn–Ag couples	dimethoxyethane or THF, −10° to room temp	cheap, works with most α,α′-dibromoketones, has been used, routinely, on the 0.1 M scale with furan as trapping agent
$Zn/(EtO)_3B$	THF, room temp, overnight	must be at least one hydrogen α to the carbonyl, has been carried out on the molar scale
Cu, NaI	MeCN, room temp to 60°, 4 h to overnight	does not work with tetrabromoacetone, produces the least electrophilic oxyallyl cation



Scheme 9.

cation is highly electrophilic, and side reactions predominate. In particular, the conjugated dieneal (**26**) has been observed as a major product, and this presumably arises via alkylation of furan with subsequent ring cleavage (Scheme 10).

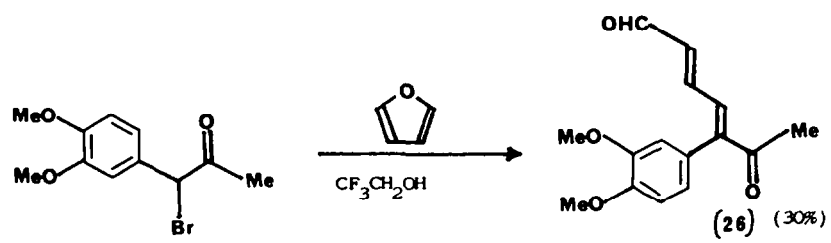
The silver salt route has also been developed by Mann and Usmani[23] and Föhlisch and co-workers.[25,26] Mann and Usmani demonstrated that oxyallyl cations can be generated from α-bromoketones upon reaction with silver tetrafluoroborate and triethylamine, either in acetonitrile or in neat furan which serves as both solvent and trapping agent.

Föhlisch and co-workers employed the more acidic γ-bromo-β-oxonitriles (**27**) in conjunction with silver oxide, again with furan as solvent and trapping agent. Satisfactory yields of cycloadducts were only obtained when the bromoketone possessed a tertiary γ-carbon or when it was mono-alkylated at both the α- and γ-carbon atoms. Föhlisch and co-workers proposed the intermediacy of the oxyallyl cation (**28**), and typical results are shown in Scheme 11.

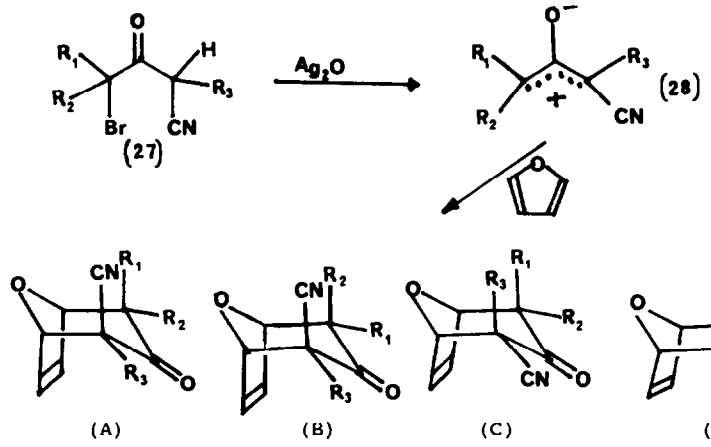
Silver perchlorate has been used by Shimizu *et al.*[27] in combination with 2-(trimethylsiloxy)allyl chlorides (**29**); and Sakurai *et al.*[28] have used the same kinds of allyl chlorides in conjunction with a $ZnCl_2$–ether adduct. In both instances the metal salt induces heterolysis with obtention of the oxyallyl cation (**30**) (Scheme 12).

Herter and Föhlisch also introduced the cheaper reagent $LiClO_4$/triethylamine (in diethyl ether)[29] for reaction with α-chloro- and α-bromoketones, presumably with the lithium oxyallyl (**19**, M = Li) as intermediate. The advantage of this method is that the course of the reaction can be followed by the appearance of the insoluble triethylammonium halides. The same reagent has been employed to good effect with 1,1-dichloro- and 1,3-dichloroketones,[30] and as usual the oxyallyl cations were trapped with furans.

However, Föhlisch's major contribution to oxyallyl methodology is undoubtedly the demonstration that oxyallyl cations can be generated from α-chloro- and α-bromoketones, simply by the addition of triethylamine (or sodium, 2,2,2-trifluoroethoxide) in methanol,[31] or better still, in 2,2,2-trifluoroethanol,[32] with a large excess of furan present as trapping agent. The method works particularly well with 1,1,3,3-tetrachloroacetone (**31**, X = Cl) and provides good to excellent yields of cycloadduct (**32**) on the multigramme scale. Subsequent reduction with activated zinc (or simply by using ordinary zinc dust and ultrasound[33]) yields 8-oxabicyclo[3.2.1]oct-6-ene-3-one (**33**) (Scheme 13).

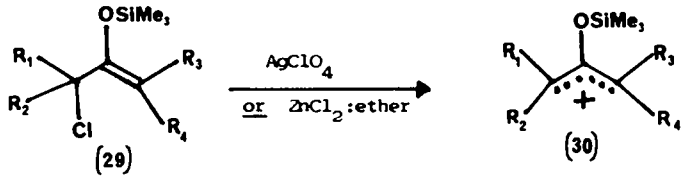


Scheme 10.

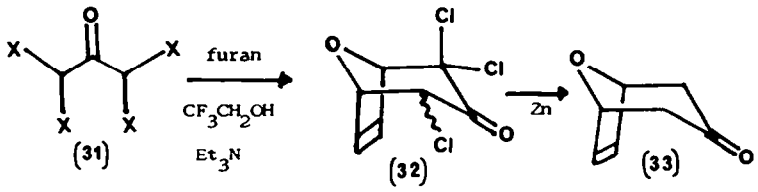


compound	ratios A	B	C	D	yields (%)
R_1,R_2 = Me; R_3 = H	-	-	100	-	31
R_1,R_3 = Me; R_2 = H	17	83	-	-	84
R_1 = Me; R_2 = H; R_3 = Et	-	80	18	2	85
R_1, R_2, R_3 = Me	-	100	-	-	75

Scheme 11.



Scheme 12.



Scheme 13.

The corresponding reactions of 1,1,3,3-tetrabromoacetone (**31**, X = Br) with diiron enneacarbonyl[16] and with triethyl borate[15] and zinc, can also be carried out on a large scale; but this ketone is much less pleasant to handle given its instability and high lachrymatory activity. In addition, tetrachloroacetone is commercially available whilst tetrabromoacetone is not. The major drawback of Föhlisch's method is the need to use a large excess of furan, thus precluding the use of anything but simple furans.

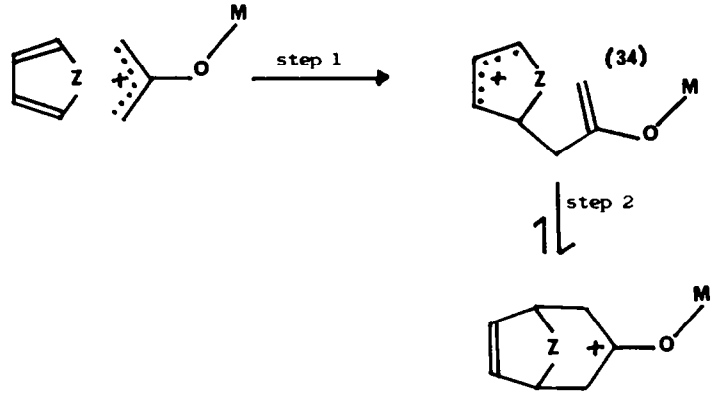
A summary of all of these methods is given in Table 2.

Table 2

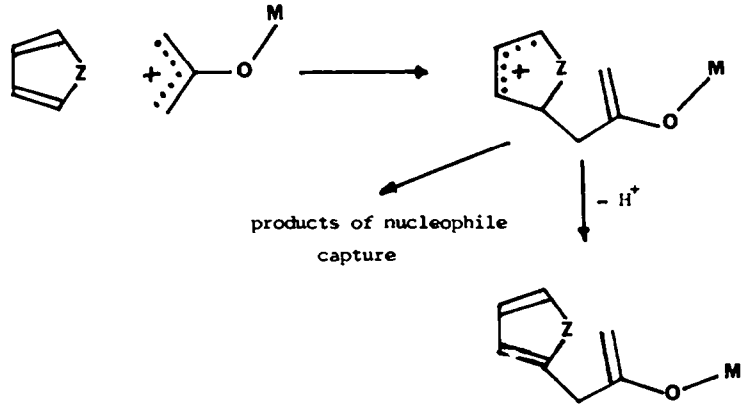
Method	Typical conditions	Comments
$AgBF_4$, Et_3N	CH_2Cl_2 or MeCN, room temp, several hours	uses α-bromoketones, expensive
Ag_2O	furan(s), CH_2Cl_2 or ether, 3–64 h, room temp	uses γ-bromo-β-oxonitriles, expensive
$LiClO_4$, Et_3N	furan(s), ether, room temp, 2 h–117 days	uses α-chloro- and α-bromoketones
$LiClO_4$	THF/ether mixtures, or $MeNO_2$, 0°, 1–2.5 h	uses silyl enol ethers of α-chloro- and α,α′-dichloroketones, substitution favoured in ether solvents
Et_3N	furan(s) and MeOH, or better CF_3CH_2OH, −20° to room temp, 1 h–29 days	cheap, α-chloro(or bromo)ketones, polychloro(or bromo)-ketones, large excess of furan(s) required, can employ commercially available tetrachloroacetone

CLASS A : concerted bond-formation

CLASS B : stepwise bond-formation



CLASS C : electrophilic addition followed by proton loss (or by nucleophile capture)



Scheme 14.

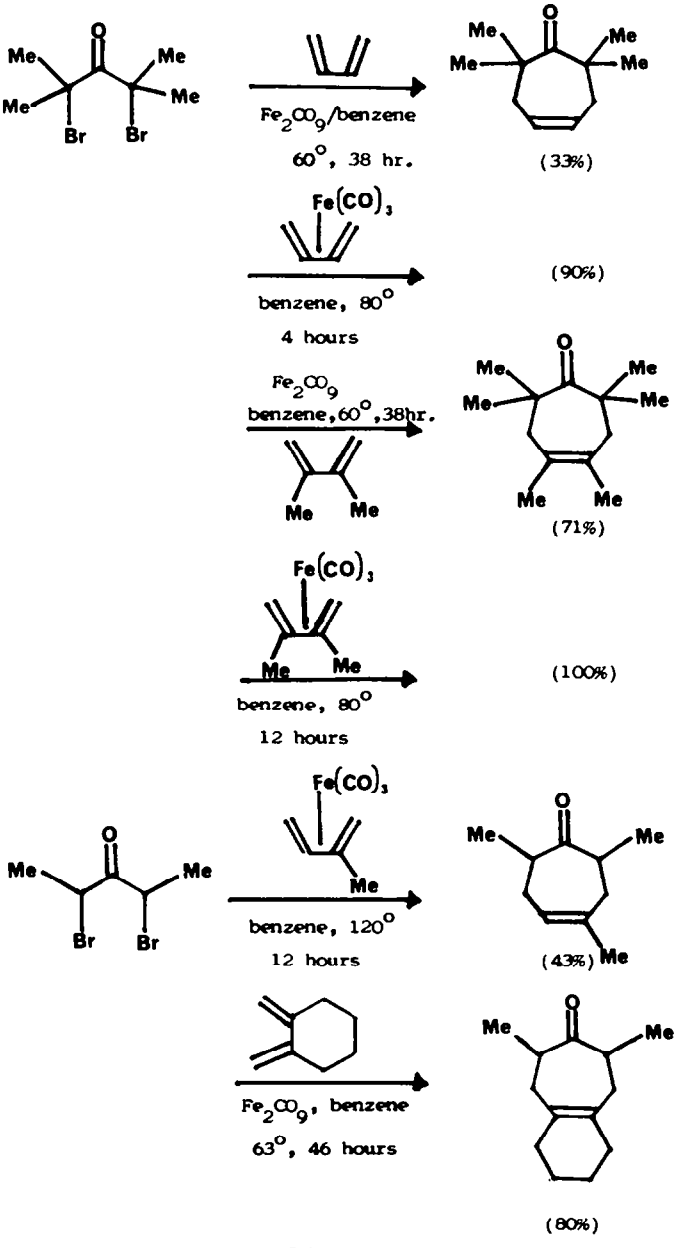
3. SYNTHESES INVOLVING OXYALLYL CATIONS

Most of the synthetic work carried out with oxyallyl cations has involved reactions with 1,3-dienes. Hoffmann has provided[2] a general classification of the reactions of allyl cations with these dienes, and this is exemplified in Scheme 14 for cyclic 1,3-dienes and oxyallyl cations.

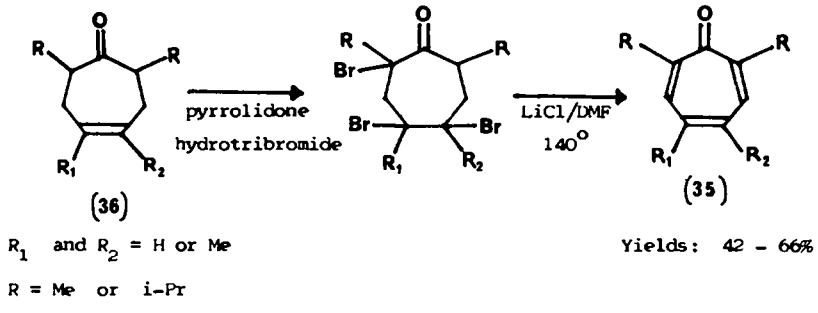
Distinction between Classes B and C will depend upon the rate constant for step 2, and its reverse, and thus upon the lifetime of the putative intermediate (**34**). The stereochemical outcome will depend upon the conformation favoured in the transition state (Class A), or upon the lifetime of intermediate **34** (Class B). Key mechanistic and stereochemical features will be discussed in the following sections, but more comprehensive discussions have been provided by Hoffmann,[2] Noyori *et al.*[34] and others.[35,36]

3.1. *Reactions with acyclic dienes*

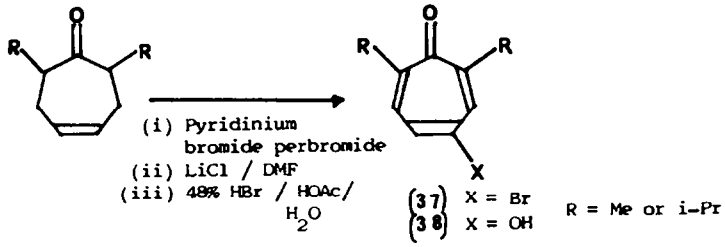
Oxyallyl cations have been generated in the presence of a variety of acyclic 1,3-dienes, and the yields of cycloadducts are generally good provided that the diene exists primarily in an *s-cis* conformation. Typical conversions, all due to Noyori and co-workers,[16] are shown in Scheme 15.



Scheme 15.



Scheme 16.



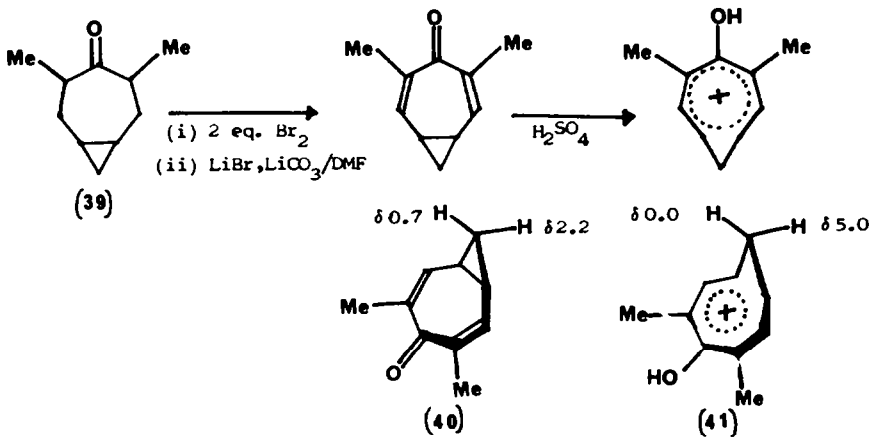
Scheme 17.

Of note are the increased yields obtained when the diene tricarbonyl complexes were employed in place of free diene, and when 2,3-dimethyl butadiene was used in place of butadiene. All of the reactions shown in the scheme were carried out on up to the 20 mmol scale.

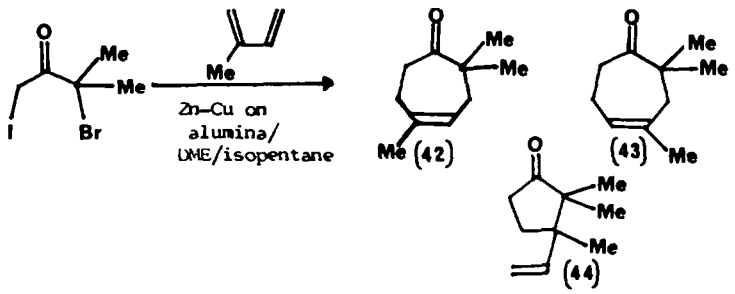
Cycloadducts of this kind have obvious potential for the production of troponoids, e.g. **35**, and Noyori and co-workers have produced a number of these[37] via bromination (pyrrolidone hydrotribromide) of cycloadducts (**36**), followed by dehydrobromination (LiCl, DMF) (Scheme 16).

If an excess of pyridinium bromide perbromide was employed, the bromotropolones (**37**) were obtained after dehydrobromination. These could be hydrolysed to γ-tropolones (**38**) using aqueous HBr, though it should be noted that all of these (reported) reactions were carried out on less than the 1 mmol scale (Scheme 17).

Finally, addition of diazomethane to cycloadduct **36** (R = Me, $R_1 = R_2 = H$) produced the bicyclo[5.1.0] system (**39**), which yielded homotropone (**40**) under the usual conditions. Treatment of this with acid led to obtention of the hydroxyhomotropylium ion (**41**) which exhibited in its NMR spectrum evidence of an induced diamagnetic ring current (Scheme 18).



Scheme 18.



Total yield: 12%

Ratio of (42):(43):(44)–54:23:23

isoprene

Fe_2CO_9 in refluxing benzene, 57°, 10 hours

(no yields cited)

Ratio of (42):(43):(44) – 46:24:30

isoprene

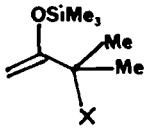
Fe_2CO_9 in refluxing benzene, 60–80°, 12 hours

(no yields cited)

Ratio of (42):(43):(44) – 28:11:61

(All of the above results are from reference 38.)

(ref.28)



X = Br

isoprene

$ZnCl_2$.ether/ dichloromethane

(42) and (43)

33% 18%

(ref.27)

X = Cl

isoprene

$AgClO_4$ on alumina, benzene, RT, 2.5hr.

or

$AgClO_4$/THF/ether 0° for 1hr.

(42) and (43)

Yield: 71%; Ratio 73:27

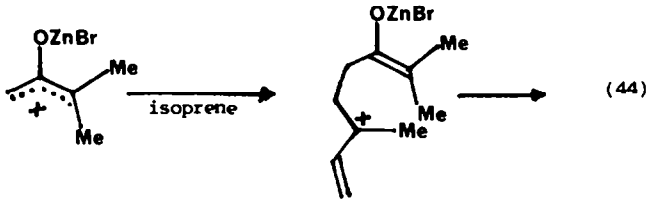
Yield: 65%; Ratio 71:29

(both gramme scale reactions)

Scheme 19.

One natural product has been the target of numerous synthetic endeavours, namely the unusual cyclic monoterpene karahanaenone (**42**), a constituent of hop oil. In each instance[27,28,38] the requisite oxyallyl was generated in the presence of excess isoprene, but in general the yields and regioselectivities were poor, and only the final entry in Scheme 19 would seem to be of any preparative value.

Isolation of **44** is of interest since this involves interception of the oxyallyl cation by a monoene rather than a diene, and Chidgey and Hoffmann have proposed[38] the sequence shown in Scheme 20 to account for this result. Other examples of this kind of reaction are given in Section 3.6.



Scheme 20.

3.2. *Reactions with carbocyclic dienes*

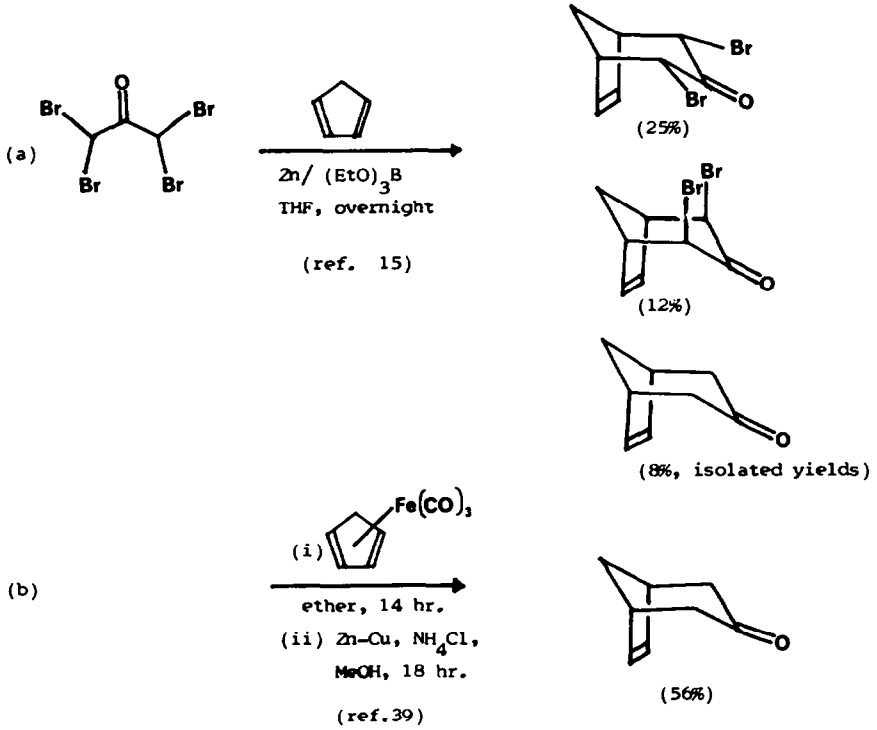
All of the main methods have been used to generate oxyallyl cations in the presence of cyclopentadiene, and representative examples of these reactions are given in Scheme 21.

It is worth studying entries (c)–(e) in some detail. In each instance only two products were obtained: **45** and **46**, the α,α- and β,β-isomer, respectively; and this has been taken as evidence that an oxyallyl cation with "W configuration" (**47**) is involved, without leakage into a "sickle configuration" (**48**) (Scheme 22). Trapping of this latter species would yield the α,β-isomer (**49**).

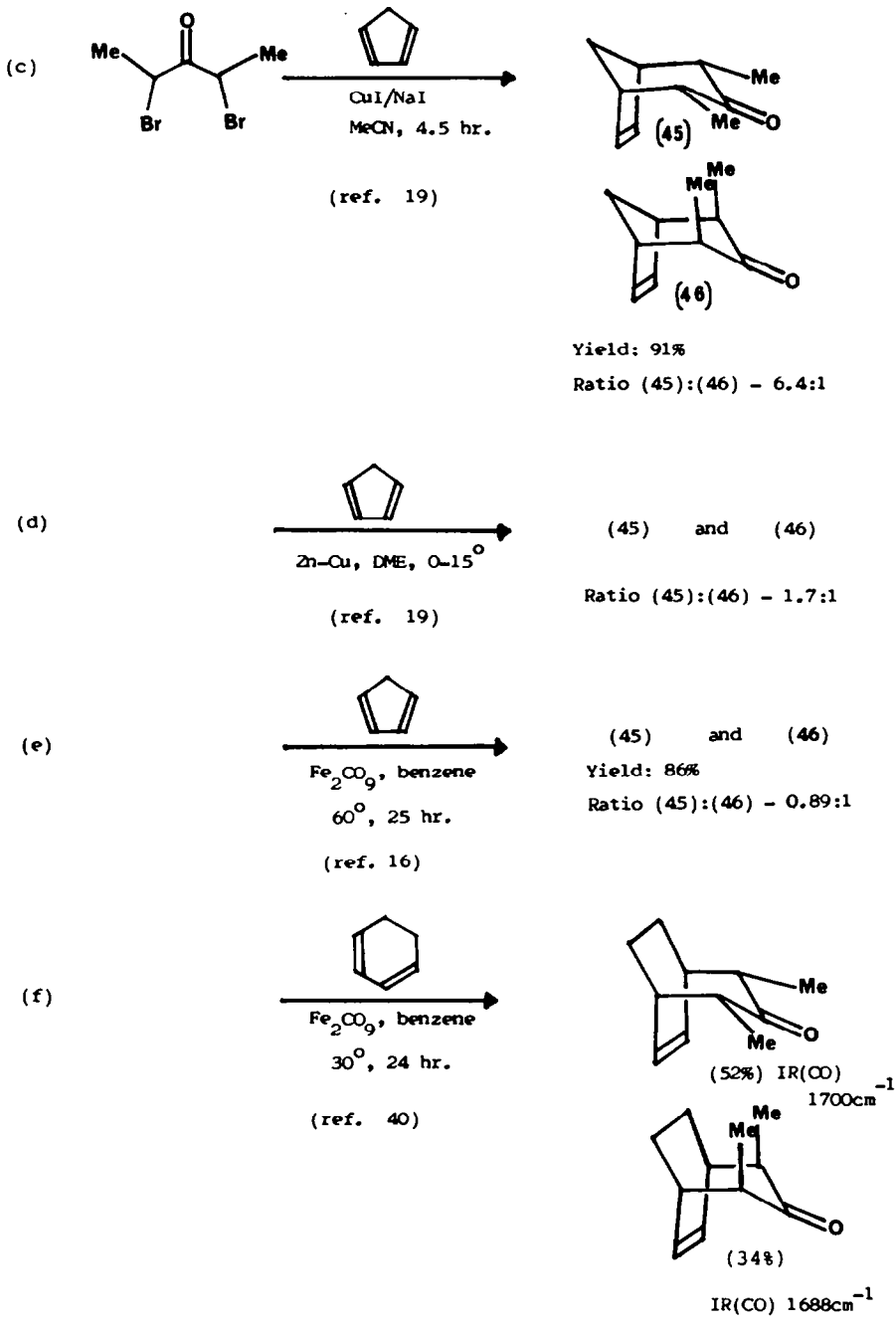
The oxyallyl cation is assumed to be trapped during a concerted process (Class A) which proceeds via compact or extended modes in the transition state (Scheme 23). Clearly the compact mode is favoured when Cu/NaI is employed, and as the oxyallyl becomes more electrophilic, the extended mode becomes more favourable.

Hoffmann[1,2] and others[27,36] have suggested a number of possible explanations for these results in terms of both secondary orbital interactions and conformational control; but regardless of the actual reason, the steric course of the cycloadditions can be controlled (at least to an extent) by a judicious choice of reagents and conditions.

The profound effect of solvent on the course (and indeed mechanism) of cycloadditions is provided by a series of reactions carried out by Shimizu *et al.*[27] A number of 2-(trimethylsiloxy)allyl chlorides were treated with $AgClO_4$ in the presence of cyclopentadiene, either in nitromethane or THF as solvent. Two informative results are shown in Scheme 24. It can be seen that in nitromethane



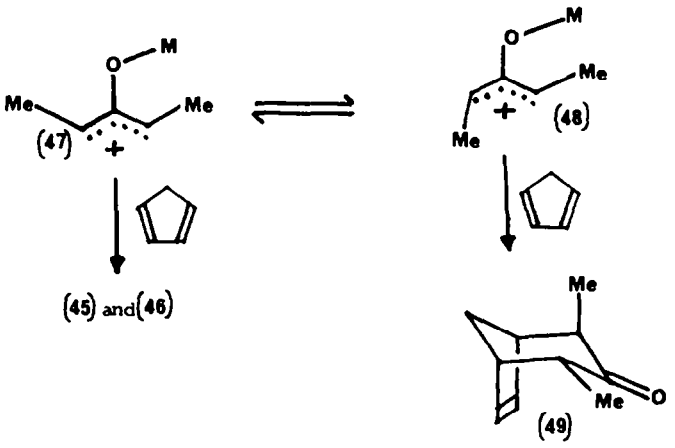
Scheme 21.



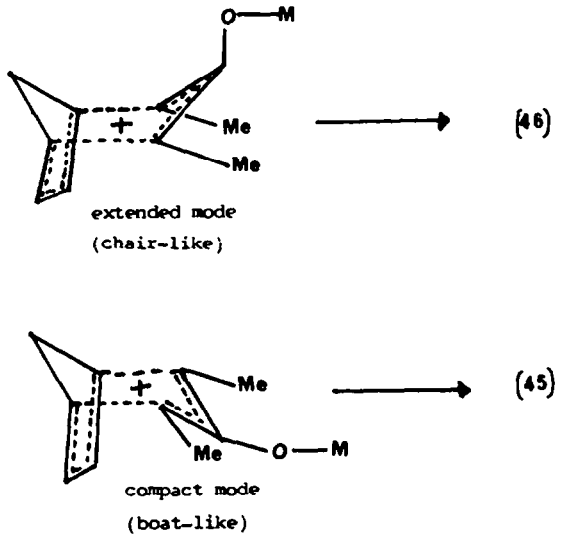
Scheme 21—(*contd.*).

a concerted process is probably involved, with a good yield of cycloadducts **50** and **51**, produced via compact and extended modes in the ratio of 71 : 29. In contrast, a stepwise mechanism is postulated for the reaction in THF, and numerous side products (substitution products ?) accompany a 1 : 1 mixture of isomeric cycloadducts. The corresponding results when furans were employed will be discussed in Section 3.4.

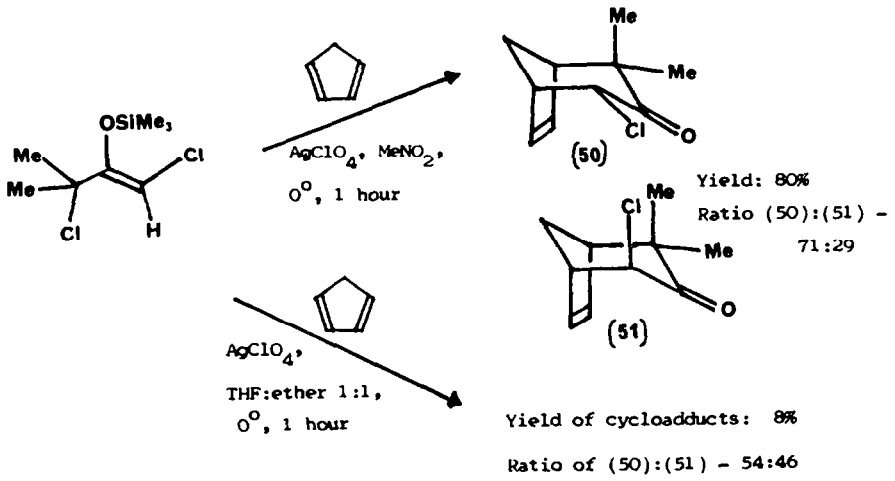
A number of fulvenes have also been employed as trapping dienes,[19] and the reactions shown in Scheme 25 are exemplary. Interestingly, there is a partial flattening of the cyclohexanone ring in cycloadduct **53**, as a consequence of the *syn*-diaxial repulsion between the methyl groups (note the smaller IR carbonyl frequency compared to that exhibited by cycloadduct **52**). A similar conformational change can be seen for the cycloadducts formed from the oxyallyl, e.g. 2,4-dibromopentan-3-one and cyclohexa-1,3-diene (entry (f) in Scheme 21).



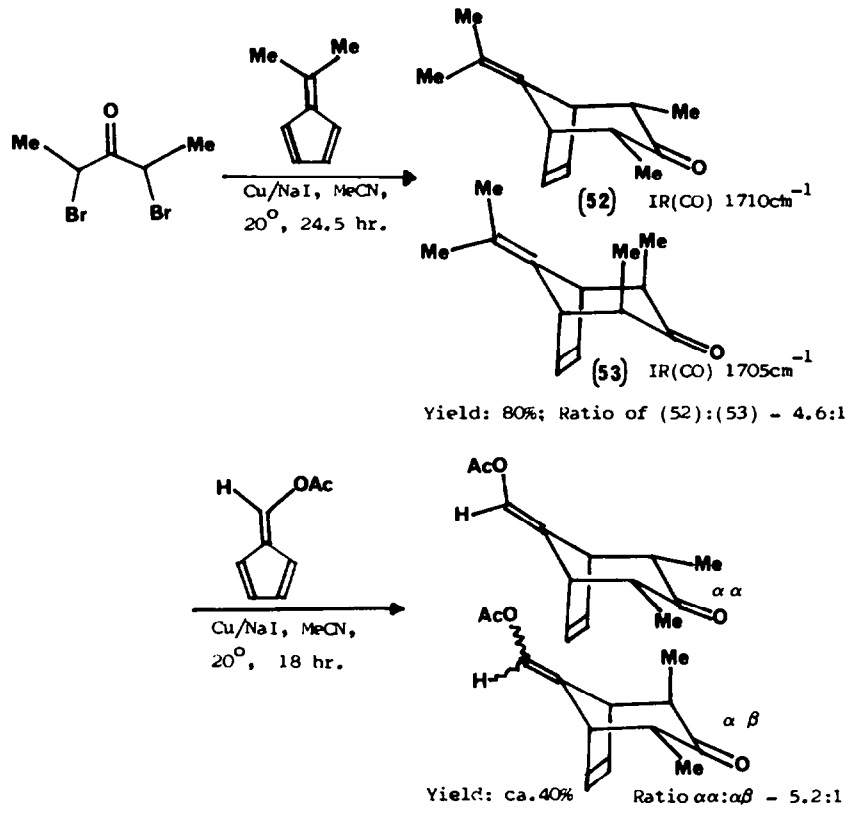
Scheme 22.



Scheme 23.



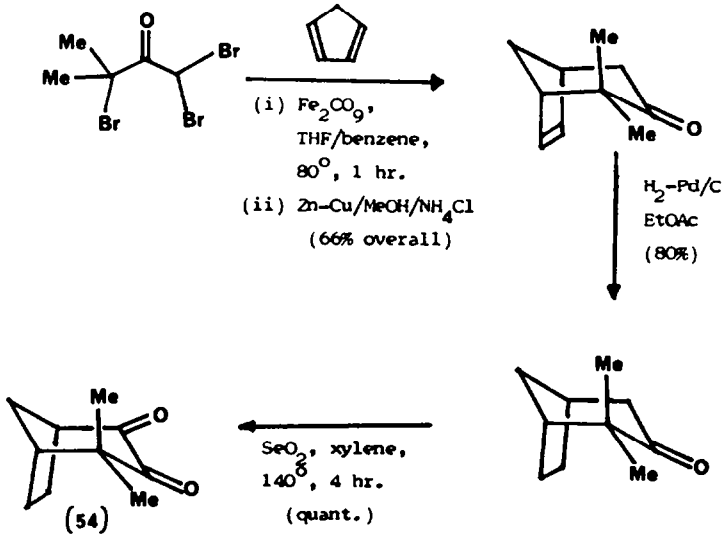
Scheme 24.



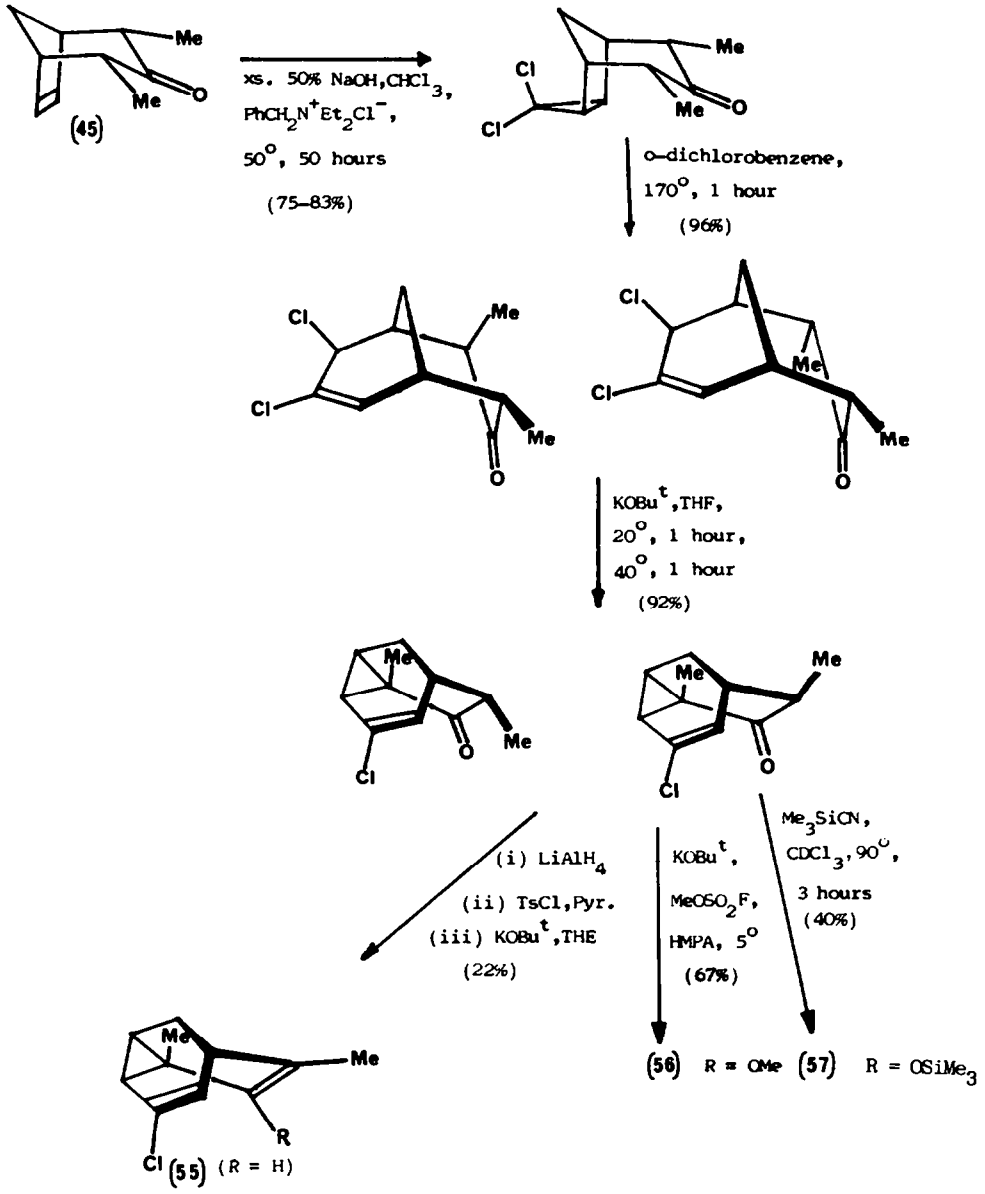
Scheme 25.

The preparative utility of these cycloadditions has yet to be tested, since few of the (reported) reactions have been carried out on more than the 1 g scale. One natural product has been synthesised, namely carbocamphenilone (**54**), a bicyclic monoterpene hitherto obtained in poor yield from camphene.[41,42] Noyori *et al.* employed the route shown in Scheme 26, though once again all of the reactions that they record were carried out on less than the 5 mmol scale.[43]

Cycloadduct **45** has been used by Hoffmann for the construction of barbaralanes (**55–57**)[44] (Scheme 27), and he notes that the synthesis was greatly facilitated by the availability of the cycloadduct in 100 g batches.



Scheme 26.



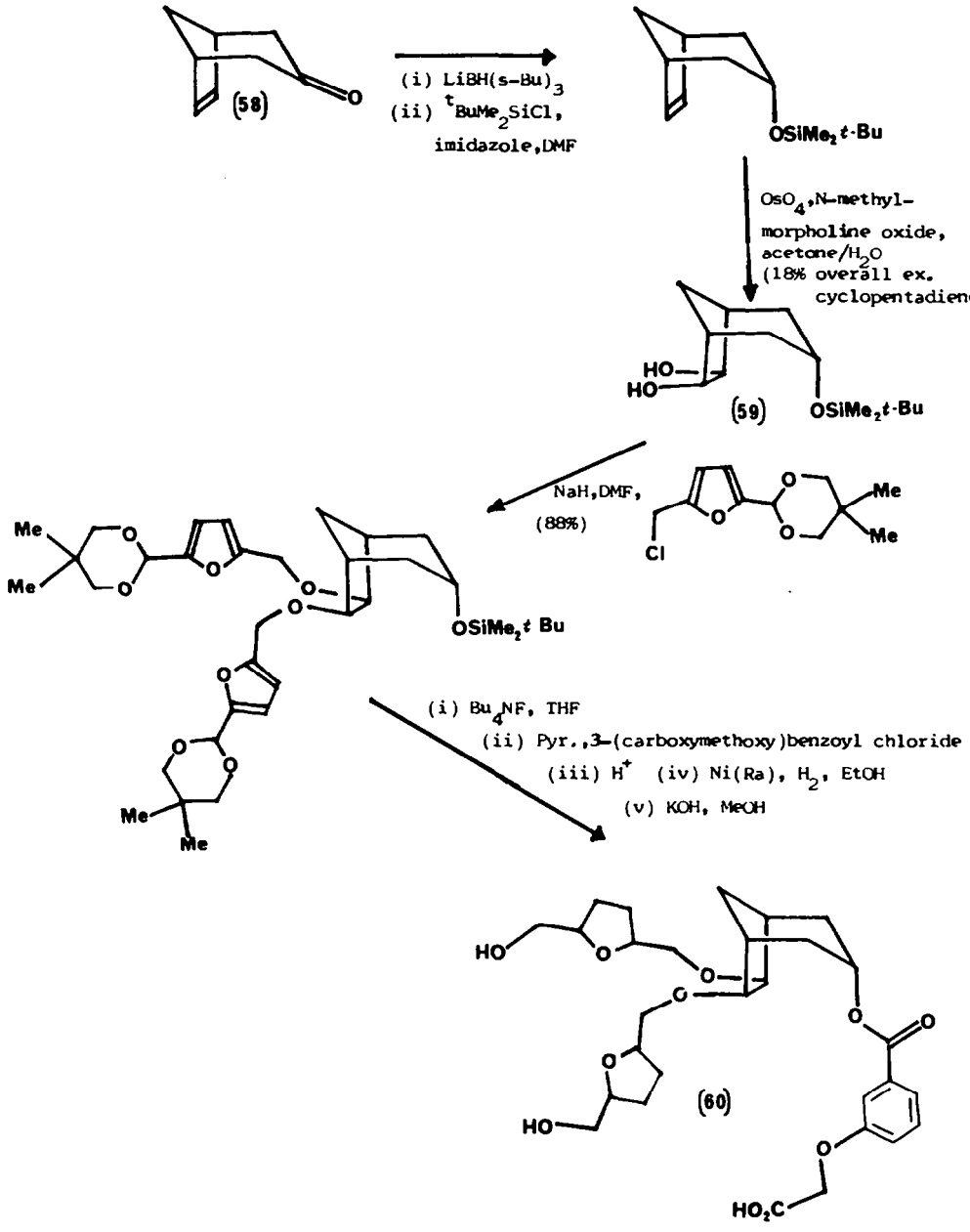
Scheme 27.

Finally, the simplest cycloadduct in this series, bicyclo[3.2.1]oct-6-en-3-one (**58**), has been reduced stereoselectively, then oxidized to yield diol **59**, and this was then converted into the novel, non-cyclic ionophore (**60**)[45] (Scheme 28). This was shown to transport Ca^{2+} ions efficiently.

3.3. *Reactions with pyrroles*

As mentioned previously, the use of the more electrophilic oxyallyl cations in conjunction with N-alkylpyrroles leads to the exclusive formation of substitution products like **61** and **62**, and the reactions shown in Scheme 29 are representative. These are formally products of a Class C process (using Hoffmann's terminology), though the known instability of the cycloadducts, e.g. **63** and **64**, especially in the presence of Lewis acids or at elevated temperatures, means that a Class B process could also be involved, with a favoured reversal of step 2 (Scheme 14).

When the copper–sodium iodide method is employed with acyclic α,α′-dibromoketones, 8-azabicyclo[3.2.1]oct-6-en-3-ones, e.g. **63** and **64**, are formed in good yields.[20] Only the α,α-dialkyl

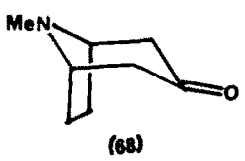


Scheme 28.

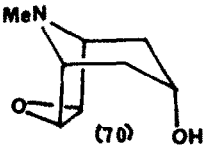
and β,β-dialkyl products are produced, and these reactions should be classified as Class A processes. Substitution products are produced when cyclic α,α'-dibromoketones are employed.[17]

In contrast, with N-carboalkoxypyrroles or N-acylpyrroles in conjunction with diiron enneacarbonyl and Zn–Cu couples cycloadducts are produced.[16,18] The same pyrroles do not react with oxyallyl cations generated using the copper–sodium iodide method. The cycloadditions show evidence of a loss of oxyallyl cation configuration (Scheme 30), with obtention of not only the α,α-dialkyl and β,β-dialkyl products, but also the α,β-dialkyl products.

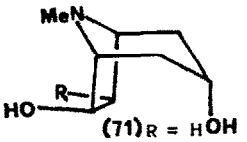
The cycloadducts have obvious structural similarities to the tropane alkaloids, and a number of natural products (and analogues) have been prepared. Thus Noyori and co-workers converted cycloadduct **65** (a mixture of α,α- and α,β-isomers) into the tropane alkaloids tropine (**66**) and pseudotropine (**67**) via the routes shown in Scheme 31.[18,46] Especially noteworthy was the



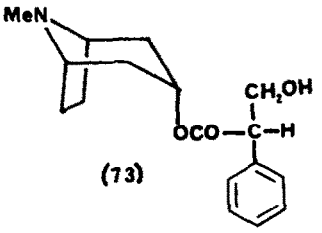
(68)



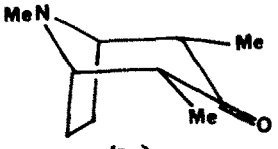
(70)



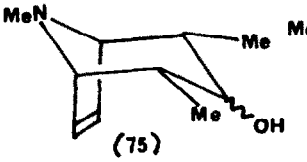
(71) R = H
(72) R = OH



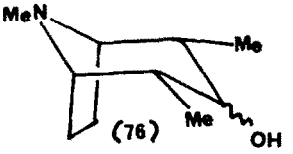
(73)



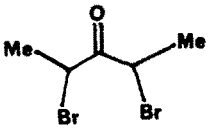
(74)



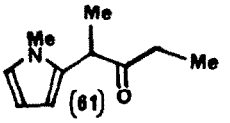
(75)



(76)



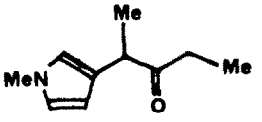
Zn–Cu, MeCN, RT, 6 hr.
(ref. 17)



(61) (40–60%)

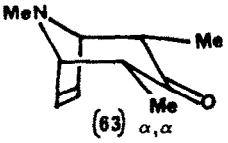
N-methylpyrrole
Fe_2CO_9, benzene,
40°, 70 hours
(ref. 16)

(61) (48%)

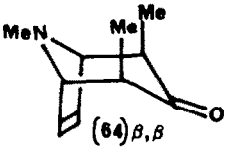


(62) (33%)

N-methylpyrrole
Cu/NaI, MeCN,
RT, 3–4 hr.
(ref. 20)

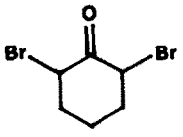


(63) α,α

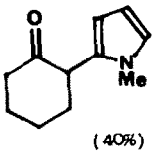


(64) β,β

Yield: 89%; Ratio (63):(64)–6:1

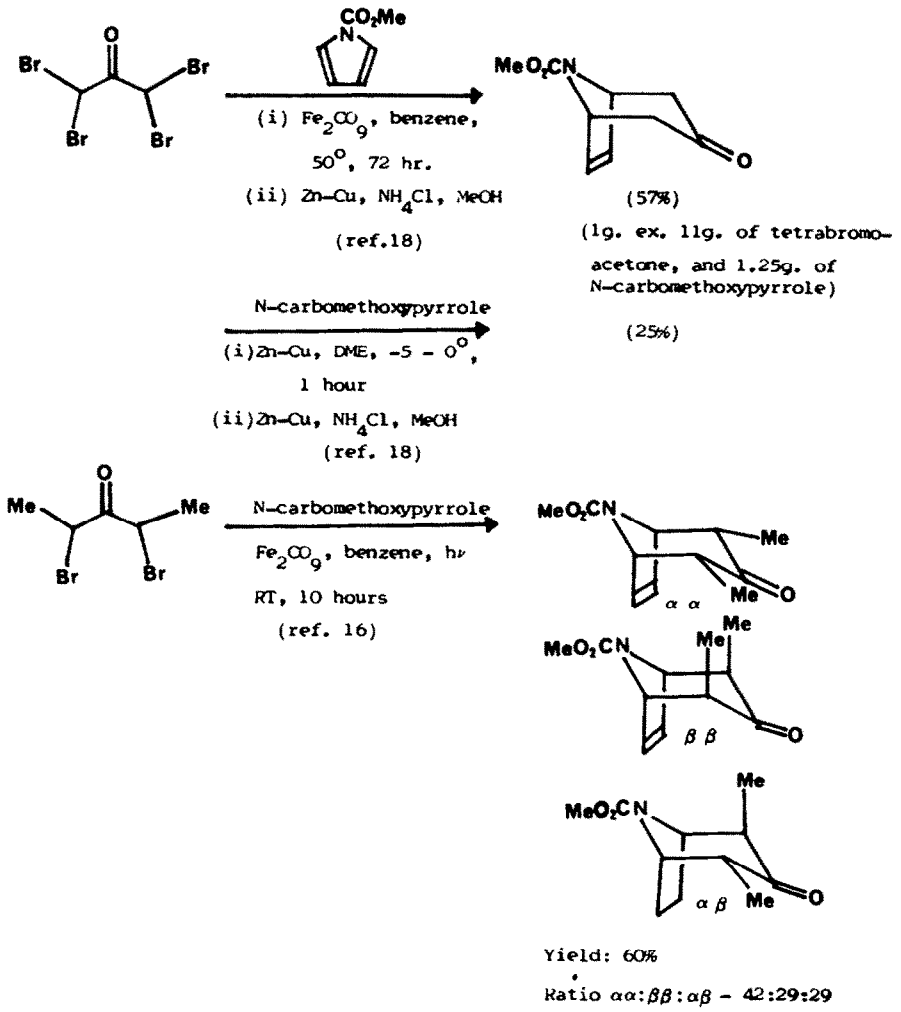


N-methylpyrrole
Cu_INaI, MeCN,
RT, overnight
(ref. 17)



(40%)

Scheme 29.



Scheme 30.

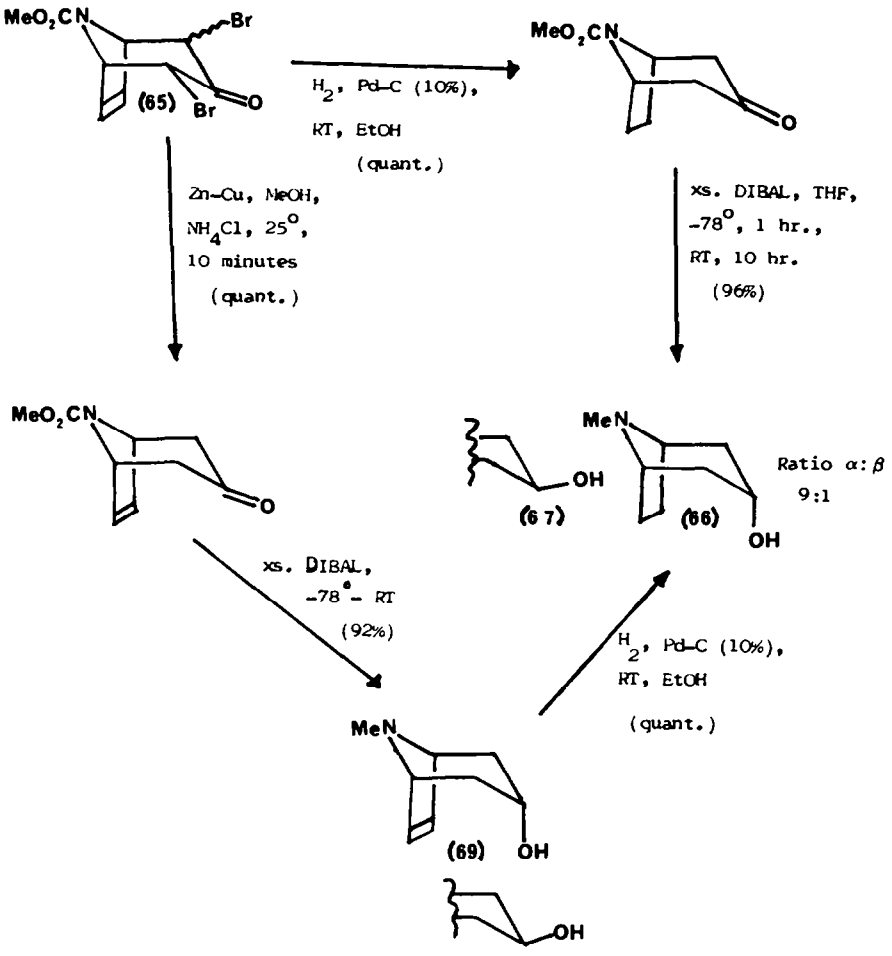
predominant production of the α-alcohols upon reduction with DIBAL. Reduction of tropinone (**68**) with either simple hydride reducing agents ($LiAlH_4$, $NaBH_4$, etc.) or with dissolving metal reagents is known to produce a predominance of the β-alcohol.[47]

Since dehydrotropine (**69**) has been converted into the alkaloids scopine (**70**), tropane diol (**71**), and teleoidine (**72**), Noyori's route provides a formal total synthesis of these compounds. He also produced hyoscyamine (**73**). Although most of the reactions reported by Noyori were carried out on less than the 1 g scale, there is no reason to believe that his routes are not viable for the production of tropane alkaloids and analogues on the multigramme scale.

The groups of Hoffmann and Mann have reported[17,20] the synthesis of a variety of tropane alkaloid analogues, e.g. **63**, **74** and the derived alcohols **75** and **76**. The latter group has also prepared esters of these alcohols, and interestingly, the benzoates of the β-alcohols possessed marked analgetic activities in a number of tests, though they were too toxic to be of clinical interest. All of the reactions were carried out on the multigramme scale, and the initial cycloaddition between N-methylpyrrole and 2,4-dibromopentan-3-one, was accomplished on the 0.1 M scale, thus offering the possibility of producing a wide variety of analogues.

3.4. *Reactions with furans*

The cycloaddition reactions of oxyallyl cations and furans have been extensively studied. All of the standard methods of generating oxyallyls have been employed, and representative examples are given in Scheme 32. With these simple systems it is clear that all of the methods can be used to good effect, and many of the cycloadditions have been carried out on the 0.1 M scale or better. Indeed,



Scheme 31.

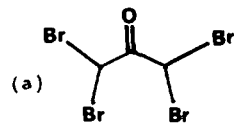
Ansell *et al.* have reported[48] production of the simplest 8-oxabicyclo[3.2.1]oct-6-en-3-one (**33**) on the 1 M scale, and Ashcroft and Hoffmann have provided full experimental details[49] for the preparation of cycloadduct **77** on the 0.1 M scale.

An analysis of the results recorded in Scheme 32 (and the many others summarized in Ref. 3) provides abundant evidence that furan usually reacts via a Class A process (concerted), and favours the compact mode for cycloaddition. The α,α-isomer, e.g. **77**, is always the major product with the Cu/NaI method, though there is considerable loss of oxyallyl cation (W-type) configuration as the species becomes more electrophilic (entries (e)–(h)) and the α,β-isomer **79** predominates when diiron enneacarbonyl is employed.

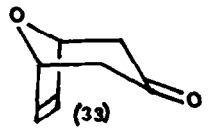
When 2-(trimethylsiloxy)allyl cations are implicated[27] (entries (i)–(l)), the course of the reaction is very sensitive to the solvent employed. Thus in nitromethane, the reactions proceed via a concerted pathway with retention of allyl cation configuration, and good yields of cycloadducts are obtained. In contrast, use of THF/ether mixtures favours a stepwise pathway, and the yields and nature of the products are dependent upon the structure of the initial silyl ether. Electrophilic substitution (Class C) becomes the main reaction in several instances.

When unsymmetrical ketones are employed in conjunction with 2-substituted furans, a degree of regioselectivity has been observed, and the examples shown in Scheme 33 represent the best that is available.

Noyori and Hayakawa rationalized their results in terms of control by the frontier molecular orbitals of the oxyallyl species (LUMOs) and furans (HOMOs),[3] though a stepwise mechanism involving intermediates like **80** should not be excluded.[54]



(a) (i) Fe_2CO_9, reflux, 48 hours
(ii) Zn–Cu, NH_4Cl, MeOH
(ref. 16)



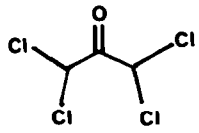
(33) (63%)

(b) furan
(i) Zn–Ag, THF, -10°, 2 hr.
(ii) Zn–Ag, THF, RT, 12 hr.
(ref. 51)

(33) (55%)

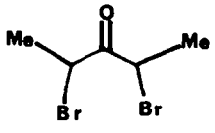
(c) furan
(i) $Zn/(EtO)_3B$, THF, RT, overnight
(ii) Zn–Cu, NH_4Cl, MeOH
(ref. 48)

(33) (54%)
(67g. ex. 1.0mol. of tetrabromoacetone, and 2mol. furan)



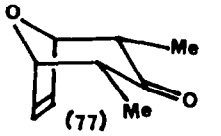
(d) furan
(i) MeOH, Et_3N, RT
(ii) Zn–Cu, NH_4Cl, overnight
(ref. 52)

(33) (45%)
(yield increased to 60%, on the multigramme scale, by using Zn/ultrasound – ref. 33)

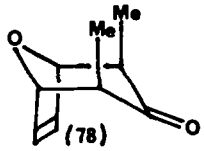


(e) Cu, NaI, MeCN, 50–60°, 4 hours (0.1M. scale)
(ref. 49)

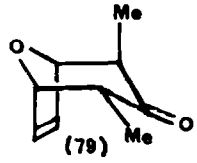
(Mann and coworkers carry out this reaction routinely on the 0.05M. scale with yields up to 80%, and with (77) comprising 95% of the product mixture)



(77) (40–48%)



(78) (5–10% typically)



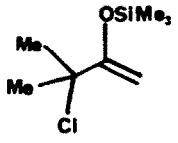
(79) (trace)

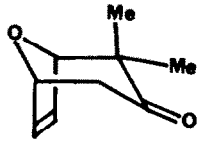
Scheme 32.

(f) furan → (Zn–Cu, DME, −10°, 1.5 hr.; ref. 8)
Yield: 85%
Ratio (77):(78):(79) – 81:10:9

(g) furan → (i) Zn–Ag, THF, −10°, 1 hr.; (ii) Zn–Ag, THF, RT, 12 hr.; ref. 51
(77) (80%)

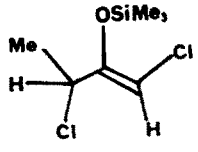
(h) furan → (Fe_2CO_9, benzene, 40°, 53 hours; ref. 16)
Yield: 90%
Ratio (77):(79) – 44:56

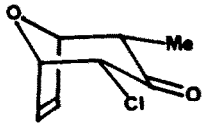
(i) 

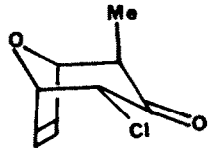
furan → ($AgClO_4$, NO_2Me, 0°, 0.5 hr.; ref. 27)


(92%)

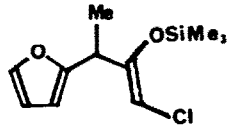
(j) furan → ($AgClO_4$, THF/ether (1:5), 0°, 0.8 hr.; ref. 27)
(85%)

(k) 

furan → ($AgClO_4$, NO_2Me, 0°, 0.5 hr.; ref. 27)


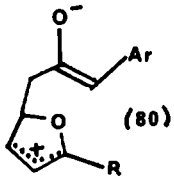


Yield: 87% Ratio: 1:1

(l) furan → ($AgClO_4$, THF/ether (1:2), 0°, 1 hour; ref. 27)


(52%)

Scheme 32—(*contd.*).



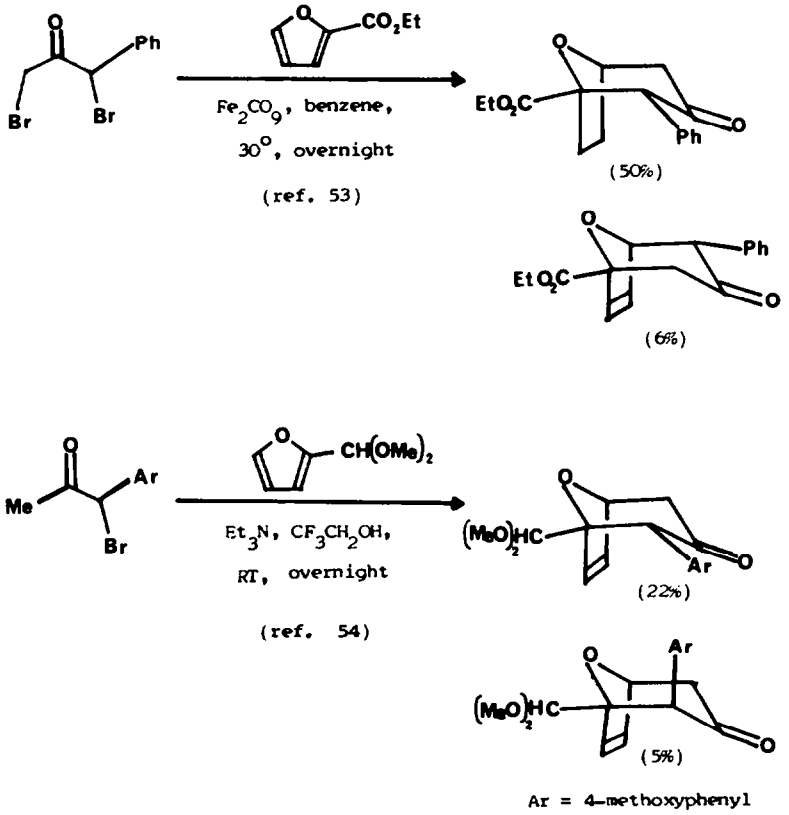
(80)

The results of Shimizu *et al.*[27] are once again consistent with a stepwise pathway in THF/ether mixtures, and with a concerted pathway in nitromethane though with poor regioselectivity.

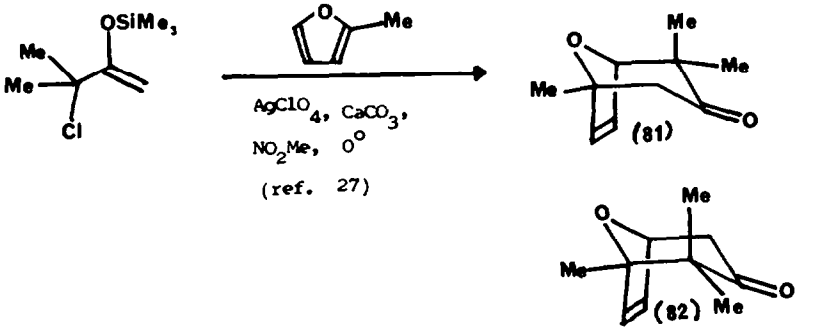
The overall impression from the results available is that regioselectivity is more pronounced when stepwise pathways are involved, though it is not always easy to predict the favoured regioisomer, and in any case, regioselectivity is only seen (to any extent) with 2-substituted furans. Complex furans almost invariably provide cycloadducts in low yield and with poor regioselectivity or stereoselectivity (Scheme 34).[19,50]

Despite these reservations, cycloaddition reactions to produce 8-oxabicyclo[3.2.1]oct-6-en-3-ones have been widely used as key steps in the synthesis of a wide variety of natural products and analogues, and these will be summarized in the following schemes.

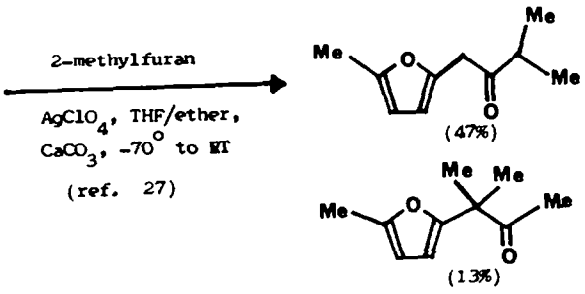
Most of the syntheses with furans have employed tetrahaloacetones or 2,4-dibromopentan-3-one as precursors of the corresponding oxyallyl cations, and historically, Noyori's route to tropones and troplones[37] was probably the first such exploitation. The cycloadduct (**83**) from tetrabromoacetone and 2-isopropylfuran was converted into the tropone (**84**), and thence into β-thujaplicin (hinokitiol) (**85**) via the routes shown in Scheme 35. Other similar conversions are also shown and lead to nezukone (**86**) and α-thujaplicin (**87**). All of the cycloadditions were carried out on the multigramme scale, but Noyori only reports experimental data for the remaining steps on less than the 0.5 g scale.



Scheme 33.



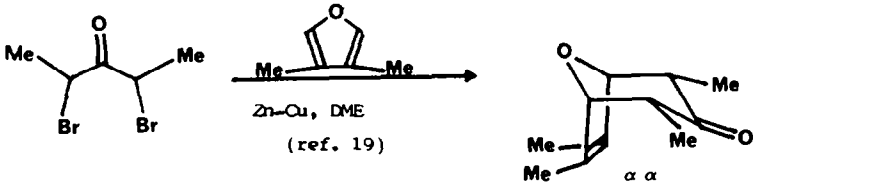
Yield:92% Ratio (81):(82)
1.9:1



(81) (38%)

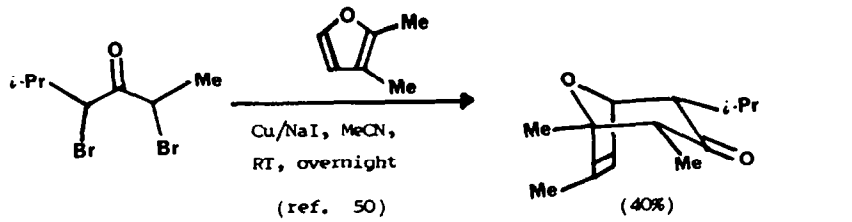
(82) (2%)

Scheme 33—(*contd.*).



and $\beta\beta$ and $\alpha\beta$ isomers

Ratio $\alpha\alpha : \beta\beta : \alpha\beta$ - 45:34:21



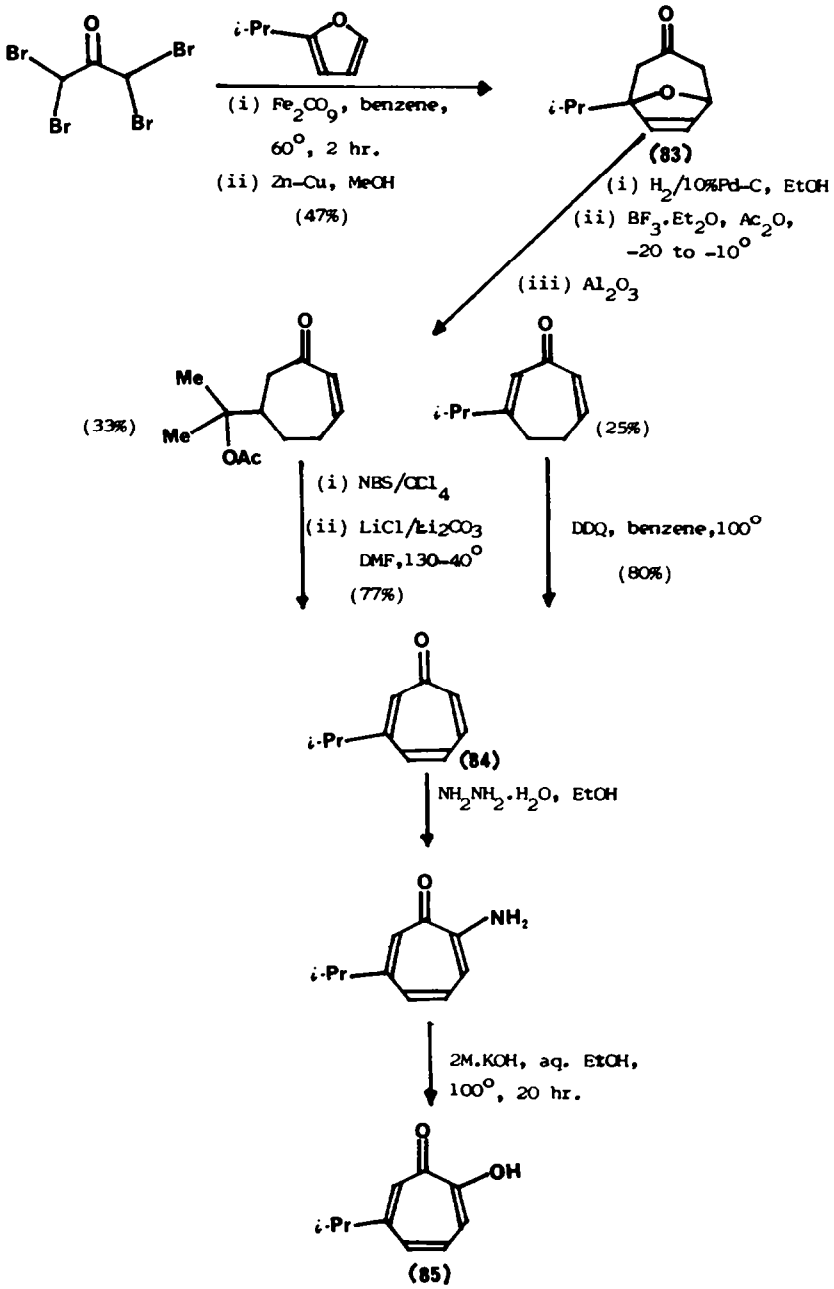
(and (35%) isolated yield of other regioisomer together with $\beta\beta$ and $\alpha\beta$ isomers as an inseparable mixture (by flash chromatography))

Scheme 34.

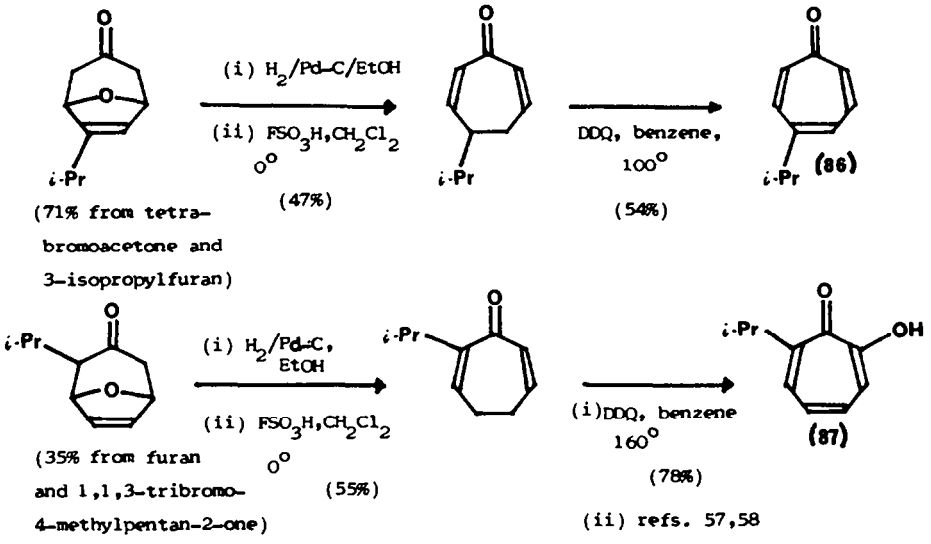
The synthesis of hinokitiol (**85**) is of particular interest since reaction of this compound with aryl aldehyde acetals yields potent antitumour agents of general structure **88** (Scheme 36).[55]

The rationale for this work was the known antitumour activity of colchicine (**89**) and its analogue (**90**),[56] and Mann *et al.* attempted to produce aryltropones of this kind via cleavage of the ether linkage in species like **91**.[24] They obtained, instead, 1-aryl-3-furylpropan-2-ones (**92**) in good yield (Scheme 37).

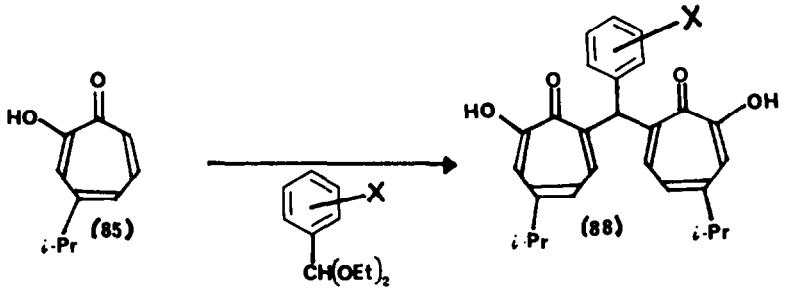
The macrocyclic antibiotics have been the subjects of numerous synthetic endeavours during the last 15 years, and a recent review of this area appeared in this journal.[59] Nonactin (**93**) has been a popular target because of its biological activity as a potassium ionophore and because of its inherent symmetry. Any synthesis must produce nonactic acid (**94**), ideally in both its (+)- and (−)-forms, since nonactin contains two of each moiety. White and co-workers synthesised (±)-nonactic acid



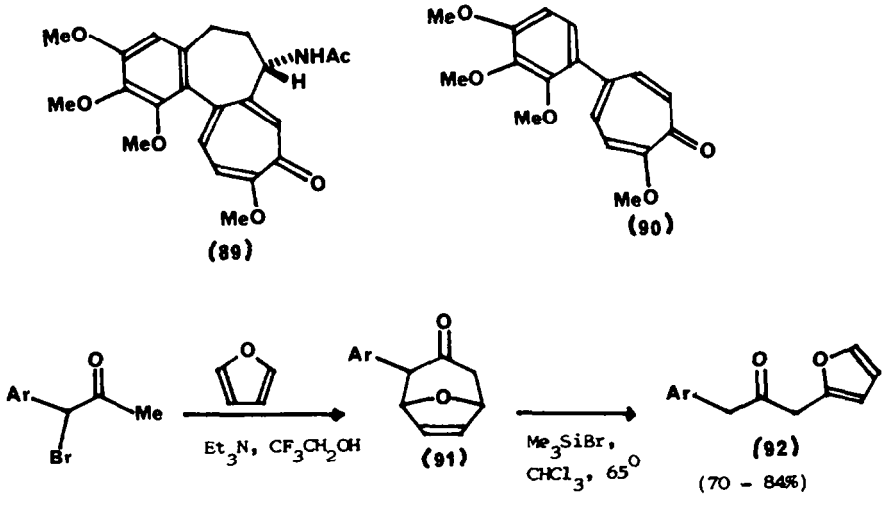
Scheme 35.



Scheme 35—(*contd.*).



Scheme 36.

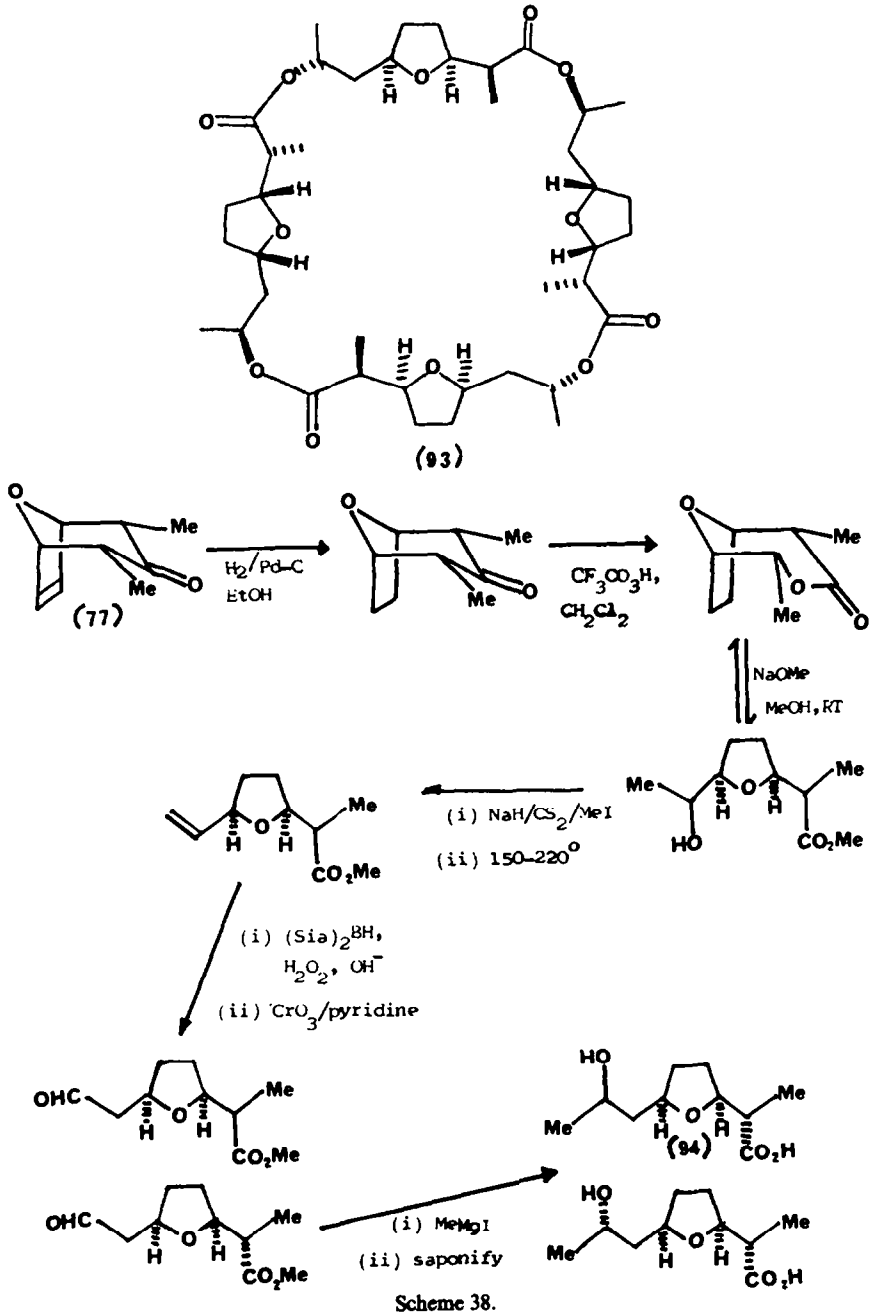


Scheme 37.

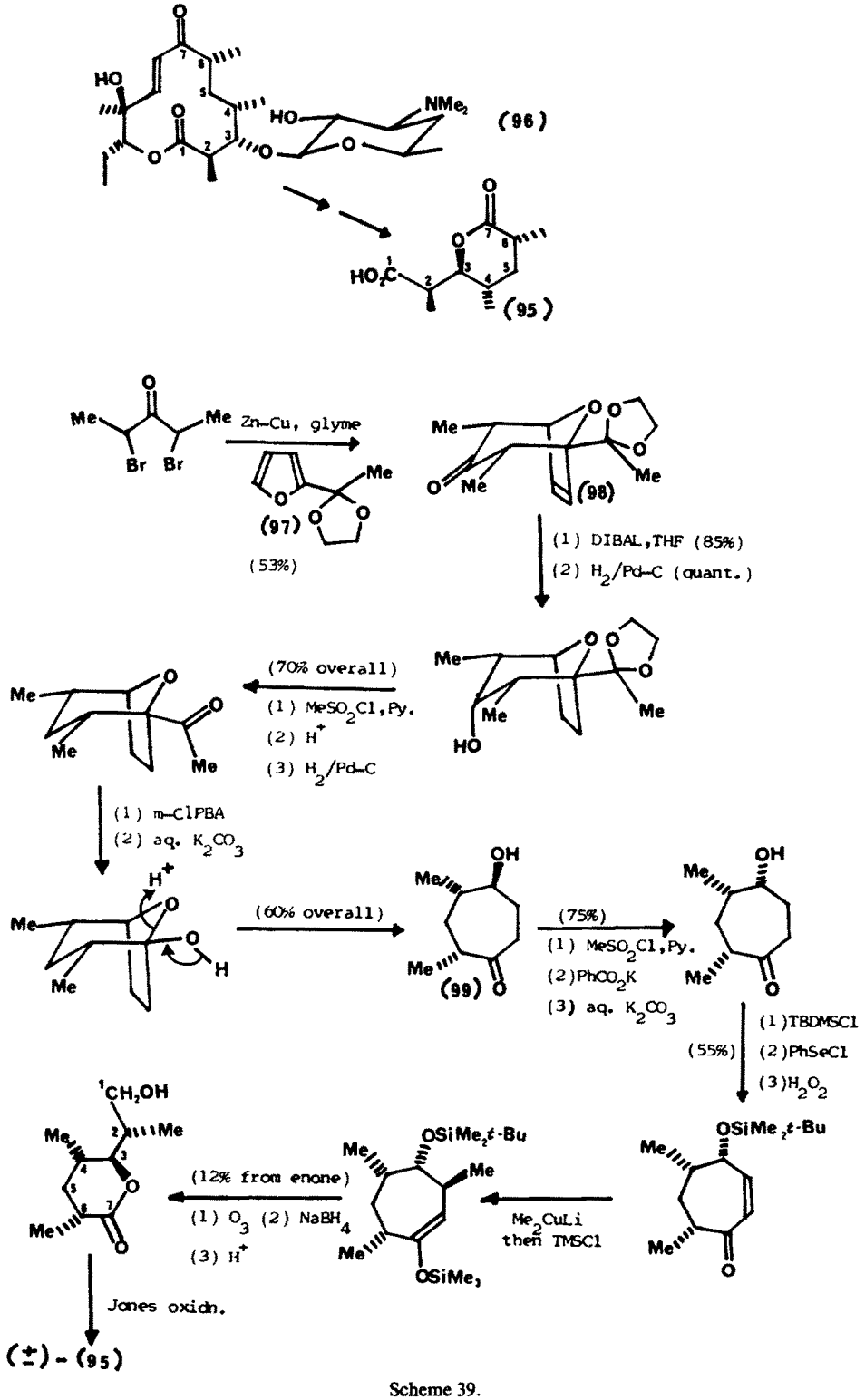
via two quite separate routes,[60] one of which involved oxyallyl methodology (Scheme 38). The sequence is fairly long and not stereoselective, but the ease with which cycloadduct **77** can be produced on a large scale[49] provides an incentive to use this as the starting material.

White and Fukuyama also employed similar chemistry for a synthesis[61] of the Prelog–Djerassi lactone (**95**), a degradation product of the macrocyclic antibiotic methymycin (**96**) (see Ref. 59 for details) that has been used by Masamune *et al.* as a key intermediate in their synthesis of the antibiotic.[62] White and Fukuyama's synthesis of **95** commenced with a cycloaddition reaction between the ethylene ketal of 2-acetylfuran (**97**) and the oxyallyl cation from 2,4-dibromopentan-3-one to produce cycloadduct **98** (Scheme 39). After reduction of the ketone and double bond, the acetyl group was converted into an acetate via a Baeyer–Villiger reaction, and the resultant bridgehead hydroxyl assisted in an ether cleavage to yield the functionalized cycloheptanone (**99**). The subsequent steps involved routine functional group manipulation, and are shown in Scheme 39.

More recently, Rama Rao *et al.* have used a similar approach for the construction of a fragment of the macrocyclic antibiotic rifamycin S (**100**) (see Ref. 59 for key information about this

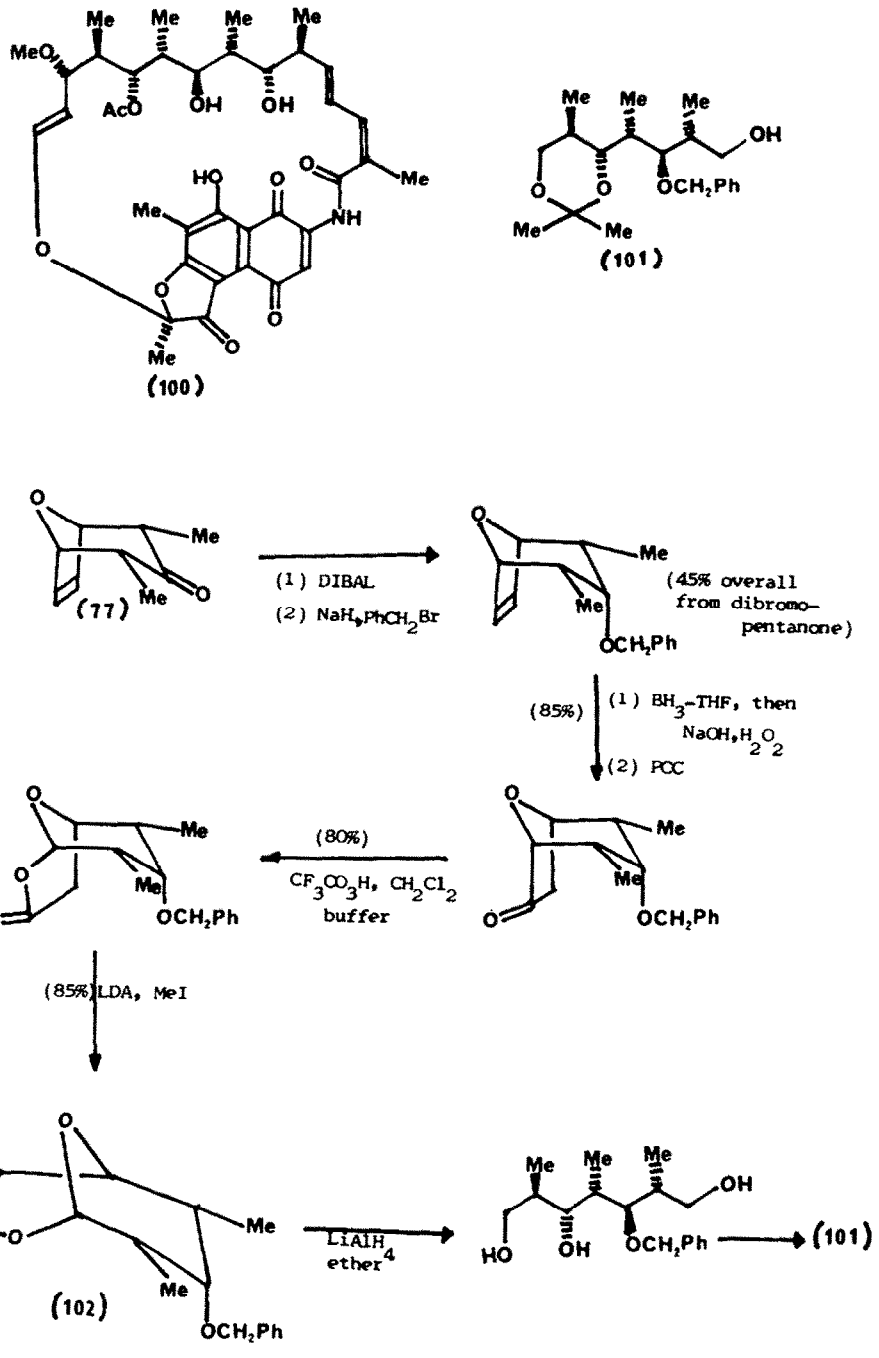


Scheme 38.



Scheme 39.

compound). They prepared the segment C-21 to C-27 (**101**) via the sequence shown in Scheme 40.[63] Once again cycloadduct **77** was employed, and this time the strategy involved cleavage of the ether bridge after initial formation of an ester (lactone) functionality at the bridgehead carbon. Base-induced cleavage was unsuccessful, but exhaustive reduction of the key intermediate (**102**) provided the desired acyclic product. This was converted into segment **101**, which possesses five contiguous chiral centres and appropriate functionality for further elaboration into rifamycin S.



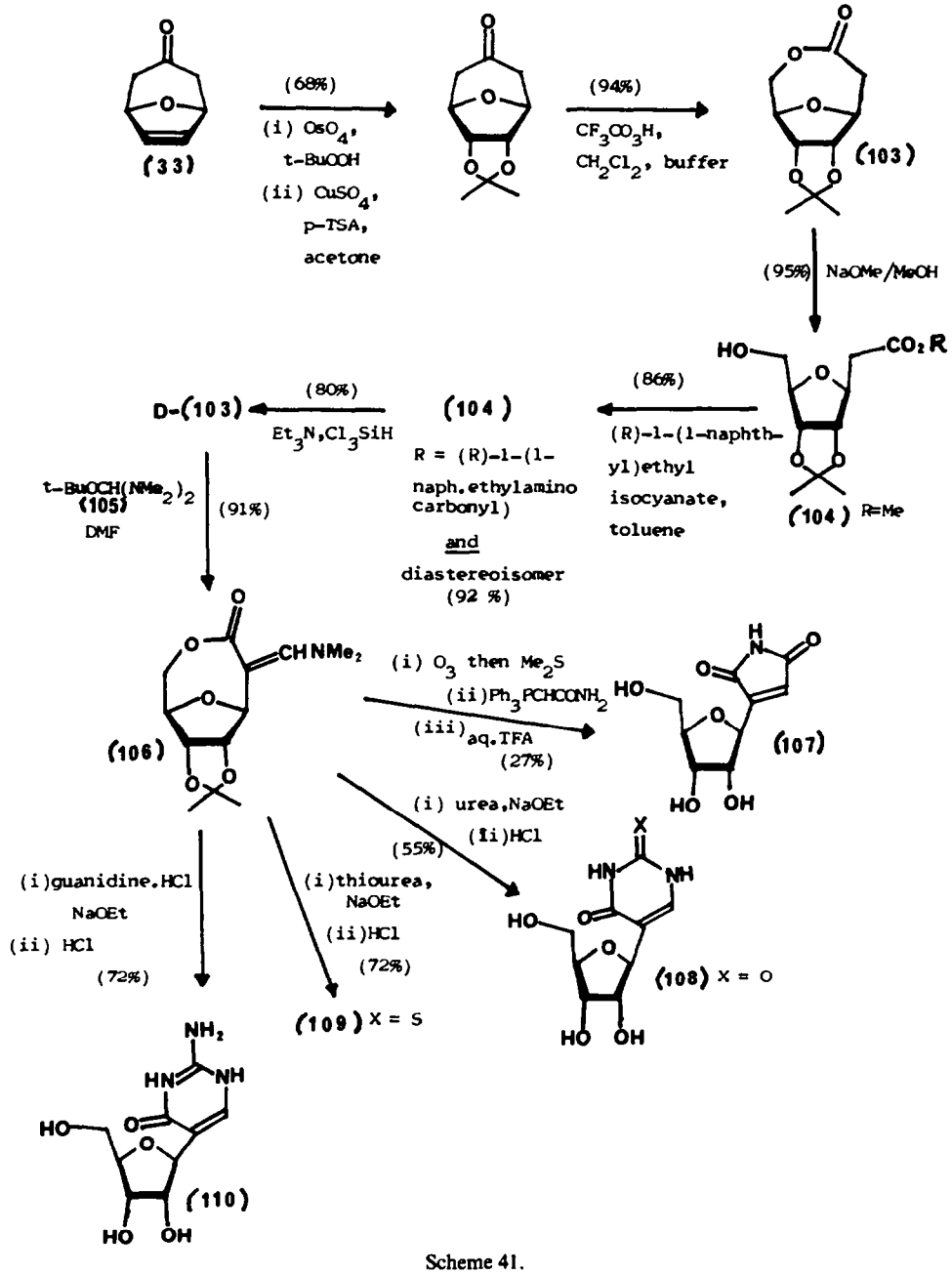
Scheme 40.

Cleavage alpha to the carbonyl group of the cycloadducts has also been widely used, most notably by Noyori and co-workers in their extensive studies on the synthesis of C-nucleosides. The key intermediate for much of this work (**103**) was synthesised via the sequence shown in Scheme 41[64] which employs a Baeyer–Villiger oxidation to effect both the desired cleavage alpha to the carbonyl and production of appropriate functionality. Resolution of lactone **103** was accomplished most effectively using Pirkle and Hoekstra's method[65] applied to seco acid methyl ester (**104**), followed by relactonization. Reaction of **103** with the Bredereck reagent (**105**)[66] provided a dimethylaminomethylene derivative (**106**), which served as a carbonyl precursor for various condensations yielding, *inter alia*, the naturally occurring C-nucleosides showdomycin (**107**)

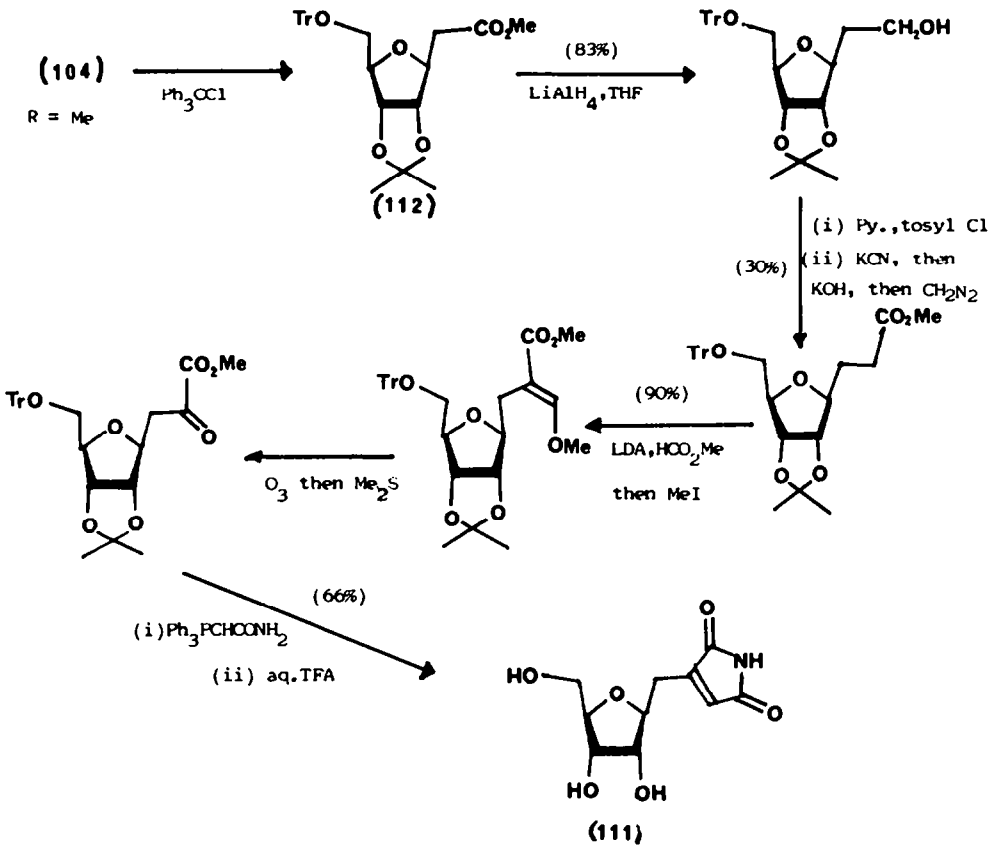
and pseudouridine (**108**), together with the novel C-nucleosides 2-thiopseudouridine (**109**) and pseudoisocytidine (**110**).

A large number of homo-C-nucleosides (with the same basic structures as those just mentioned), e.g. homoshowdomycin (**111**), were also prepared, via chain extension of the hydroxyester (**112**) (Scheme 41).[67]

Noyori *et al.* also studied[68,69] the effect of substitution at the C-5 and C-6 positions of oxabicycle **113** upon the regioselectivity of the Baeyer–Villiger reaction. The production of lactones **114α** and **α′**, or lactones **115α** and **α′** from cycloadduct **116** is shown in Scheme 43, and the results of these experiments are summarized in Table 3. The relative α′-directing abilities of the various substituents are in the order: $OSO_2R > OCOR > OR$; $OSO_2CF_3 > OSO_2Me$; $OCOCF_3 > OCOC_6H_5 > OCOCH_3$. Noyori and co-workers suggest that these results can be understood in terms of the greater decrease in electron density at the α-positions relative to that at the α′-positions in



Scheme 41.



Scheme 42.

the tetrahedral intermediates **117** and **118**. They used this information to good effect for the construction of a large number of C-nucleosides bearing substituents in the ribose ring.[70]

Most of these syntheses have been carried out on the multigramme scale, and the vast amount of work reported by Noyori and co-workers during the last 7 years concerning C-nucleoside synthesis, represents the most extensive use to date of oxyallyl methodology.

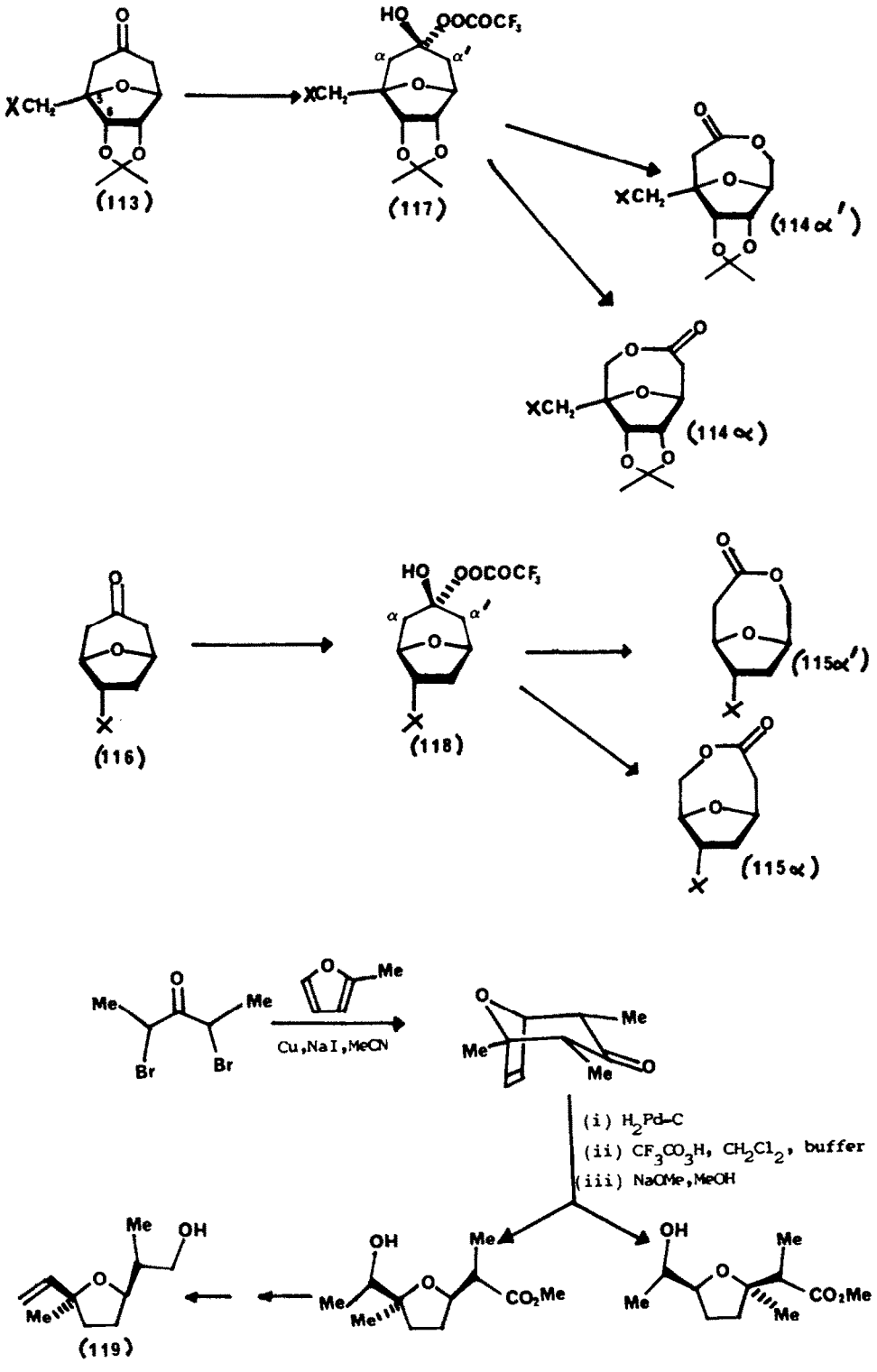
A similar approach using the Baeyer–Villiger reaction has also been used by Hoffmann *et al.*[71] for their synthesis of lilac alcohol (**119**) (Scheme 43).

An alternative strategy for cleavage alpha to the carbonyl in cycloadducts employs the Beckmann rearrangement, and in its simplest form the reduced cycloadduct (**120**) can be converted into the disubstituted tetrahydrofuran (**121**), and thence into the muscarine analogue (**122**)[72] (Scheme 44).

A more complicated sequence (Scheme 45) was carried out independently by the groups of Glass[73] and Wilson,[74] to produce the tricyclic ring system of the Lolium alkaloids, e.g. loline (**123**),

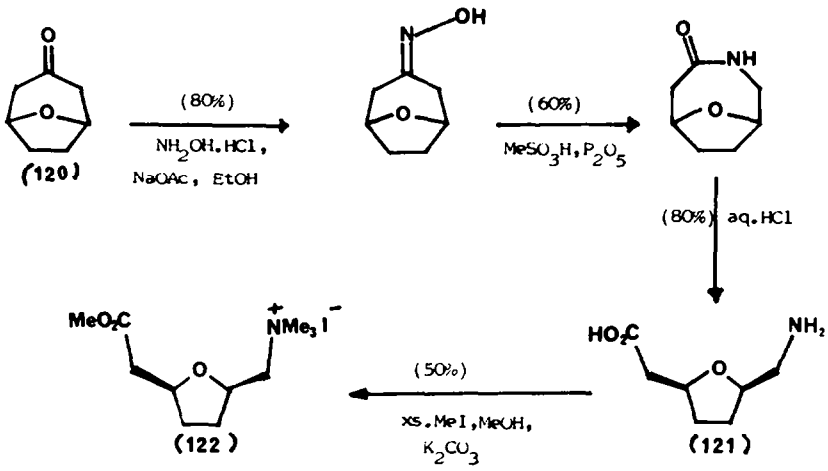
Table 3

X	(114α)/(114α′)	(115α)/(115α′)
$OSiMe_2Bu^t$	55:45	—
H	53:47	—
n-Bu	50:50	—
OCH_2Ph	48:52	30:70
OCOMe	35:65	46:54
$OCOBu^t$	31:69	35:65
OCOPh	28:72	35:65
$OCOCF_3$	23:77	—
OSO_2Me	19:81	—
OSO_2CF_3	14:86	—



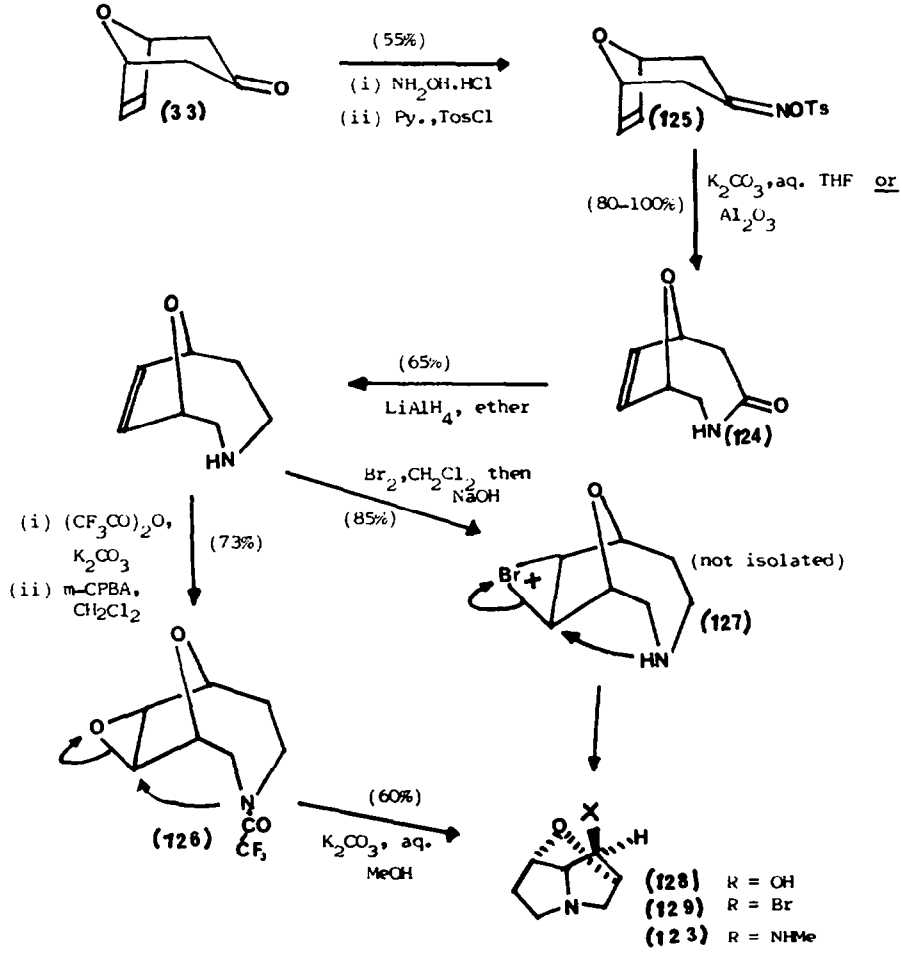
Scheme 43.

which are complex pyrrolizidine alkaloids. Both groups prepared the bicyclic amide (**124**) from cycloadduct **33** using the Beckmann rearrangement of oxime tosylate (**125**). It is worth noting that this process was carried out under very mild conditions. Subsequent reduction and cyclization via epoxide **126**, or bromonium species **127**, yielded the lolium-type tricycles **128** and **129**, respectively. Attempts to replace the hydroxyl or bromide by amines were unsuccessful.

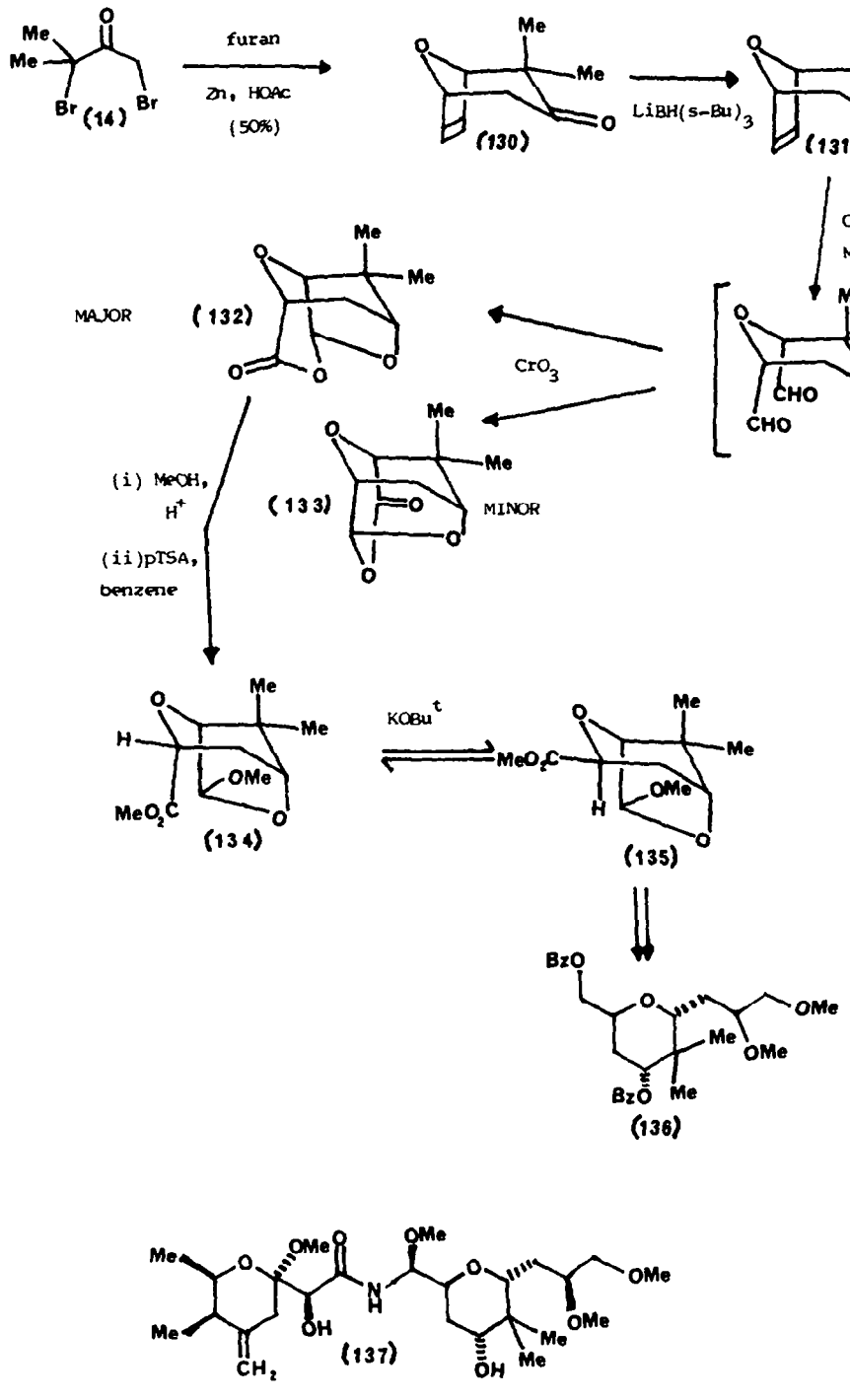


Scheme 44.

Tricyclic structures derived from 8-oxabicyclo[3.2.1]oct-6-en-3-ones have also featured in Meinwald's synthesis of the insect defence substance pederin,[75] and in the production of analogues of thromboxane A_2 by Bowers and Mann.[76] Both synthetic approaches rely upon the facility with which the carbonyl of the oxabicycles can be reduced stereoselectively to yield predominately the axial (α) alcohol. Thus in Meinwald's synthesis, cycloadduct **130** (from furan and the oxyallyl derived



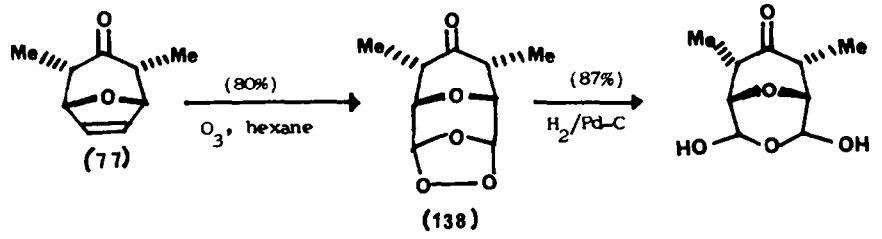
Scheme 45.



Scheme 46.

from 1,3-dibromo-3-methylbutan-2-one **14**), was reduced with lithium tri-*sec*-butylborohydride to produce exclusively the α-alcohol (**131**). Ozonolysis and subsequent oxidation then provided a mixture of lactones **132** and **133** via the sequence shown in Scheme 46.

The major product was hydrolysed with acidic methanol, then recyclized with *p*-TSA in dry benzene to produce the ester acetal (**134**). This possesses an axial ester group, but epimerization was surprisingly difficult, and a mixture of axial and equatorial (**135**) esters was obtained under all conditions. The ester **135** was subsequently elaborated, to yield the key intermediate (**136**), using standard methodology. Pederin itself (**137**) has the distinction of being the most complex, non-

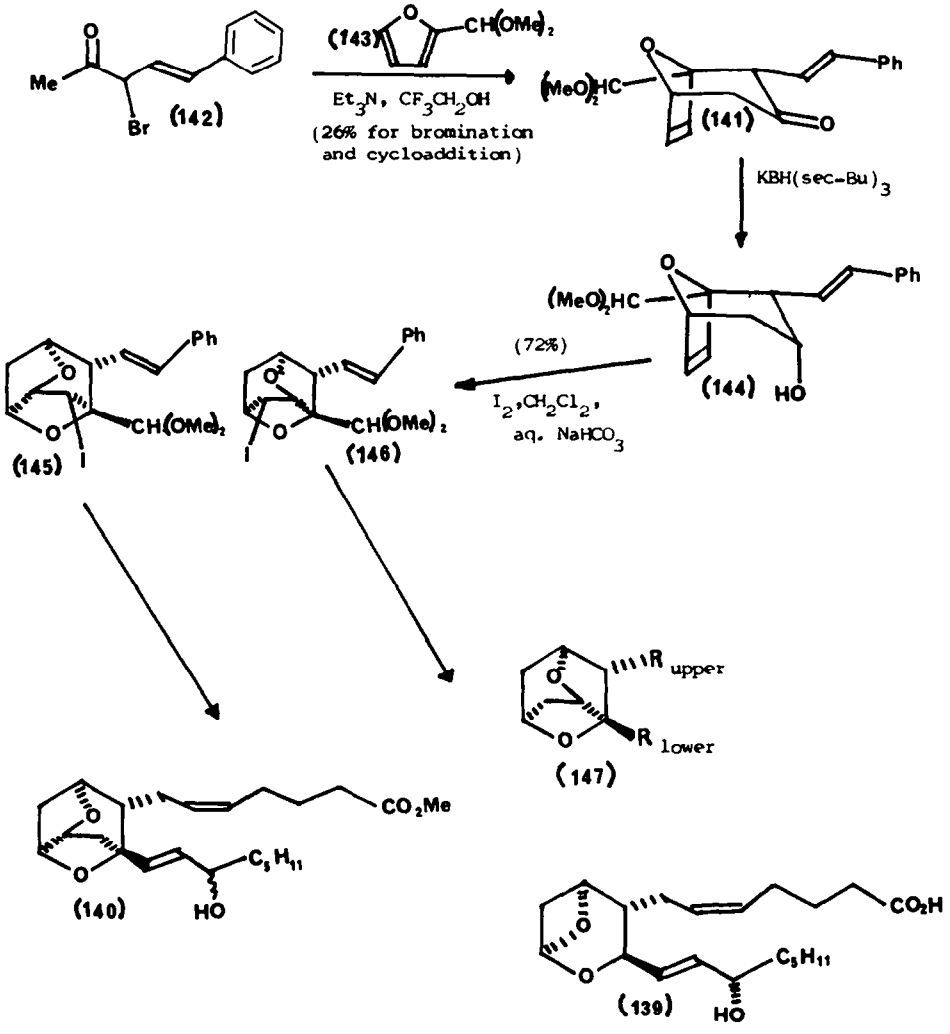


Scheme 47.

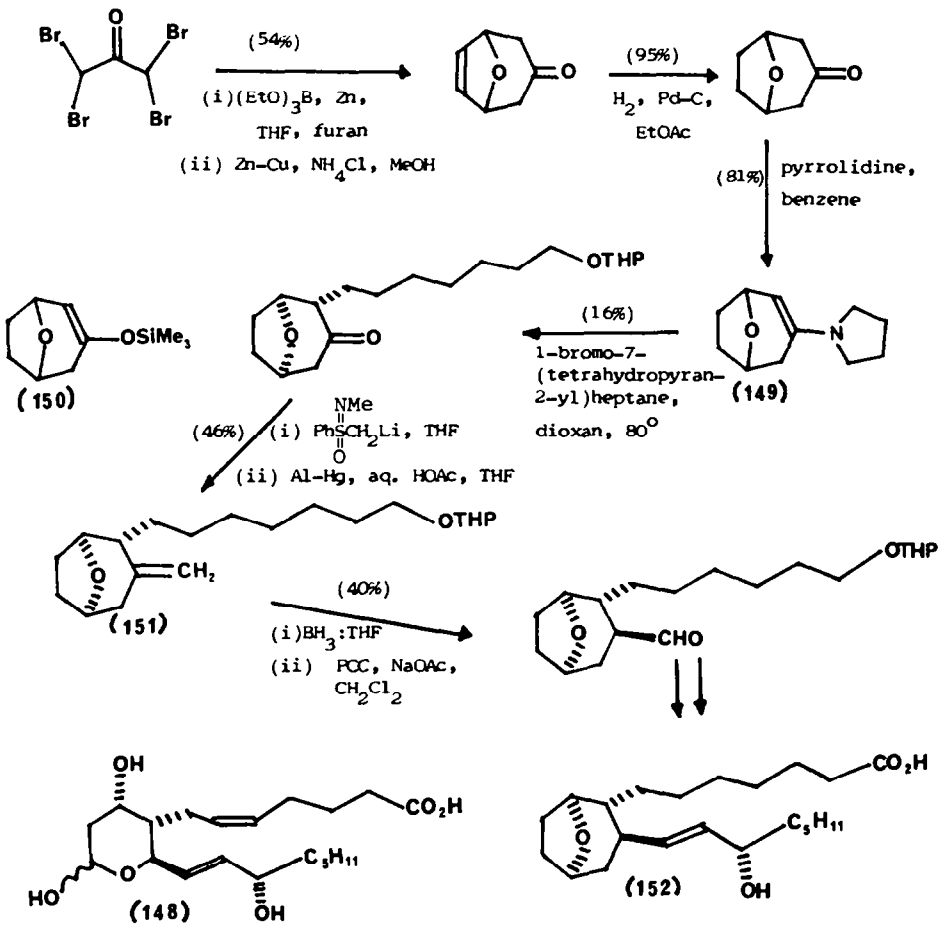
proteinaceous insect defence substance thus far isolated, and its structure was only fully elucidated in 1968.[77]

It is interesting to note that attempts by Cummins *et al.*[78] to accomplish an ozonolytic cleavage of cycloadduct **77**, led to the exclusive obtention of the crystalline ozonide (**138**). This was surprisingly stable, and an X-ray crystal structure was determined, though it could be converted into the anticipated products upon reduction (Scheme 47).

Several analogues of thromboxane-A_2 (**139**), e.g. **140**, were prepared from cycloadduct **141** via the sequence shown in Scheme 48.[76] The cycloaddition itself between the oxyallyl cation from 1-phenyl-3-bromopent-1-en-4-one (**142**) and furfural dimethylacetal (**143**) yielded predominantly the



Scheme 48.



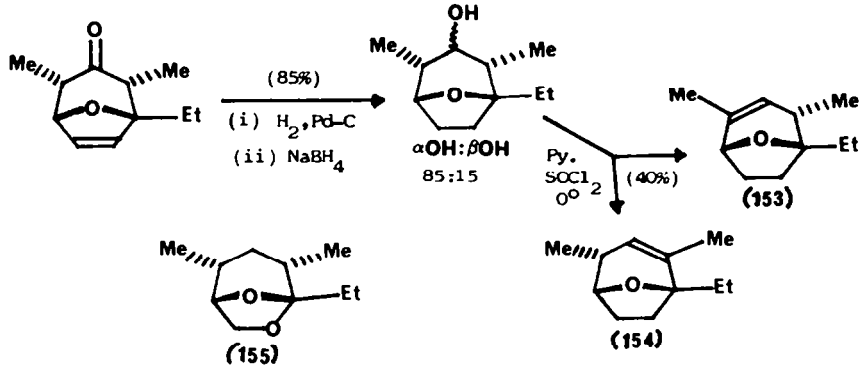
Scheme 49.

regio- and stereoisomer (**141**), though the (non-optimized) yield was not very good. It was reduced stereoselectively with potassium tri-*sec*-butylborohydride to yield the axial alcohol (**144**), and this was cyclized via iodoetherification to produce the tricyclic iodides (**145** and **146**). These were separately converted into the TXA_2 analogues (**140** and **147**) (as mixtures of their C-15 epimers) using standard prostanoid methodology. Both analogues possessed similar biological activities to those exhibited by TXA_2,[79] that is they caused aggregation of (rabbit) blood platelets and were vasoconstrictive.

An analogue of the related prostanoid, thromboxane-B_2 (**148**), has been produced by Ansell *et al.*,[48] and their initial cycloaddition (Scheme 49) was carried out on the molar scale! Introduction of the C-1 to C-7 side chain was effected under stereochemical control by alkylation of the enamine (**149**). The yields obtained with a variety of alkyl halides were consistently low, and these results parallel those of Mann and co-workers[54] in their attempts to alkylate the same ketone. These latter workers subsequently solved the problem by alkylating the enol silyl ether (**150**) with a number of alkyl halides, and obtained good yields of the desired products. Ansell *et al.* completed their synthesis via the α-methylene species (**151**), and elaboration of the C-13 to C-20 side chain. Analogue **152** exhibited weak vasoconstrictive activity, but did not cause aggregation of human blood platelets.

A few syntheses have been reported in which the basic oxabicyclic structure is retained, but the carbonyl group is removed. Thus a synthesis of the oxabicyclo[3.2.1]octenones (**153** and **154**) proceeded via reduction of the ketone and dehydration[72] (Scheme 50). The compounds are analogues of the insect aggregation compound α-multistriatin (**155**) (from the European elm beetle *Scolytus scolytus*[80]), and possessed quite marked activities as aggregation substances for this species of beetle.

Alternatively,[50] deoxygenation of cycloadduct **156** via the xanthate (**157**)[81] proceeded in excellent yield to produce an oxabicyclo[3.2.1]octane. Reaction of this with chlorosulfonyl isocyanate, with



Scheme 50.

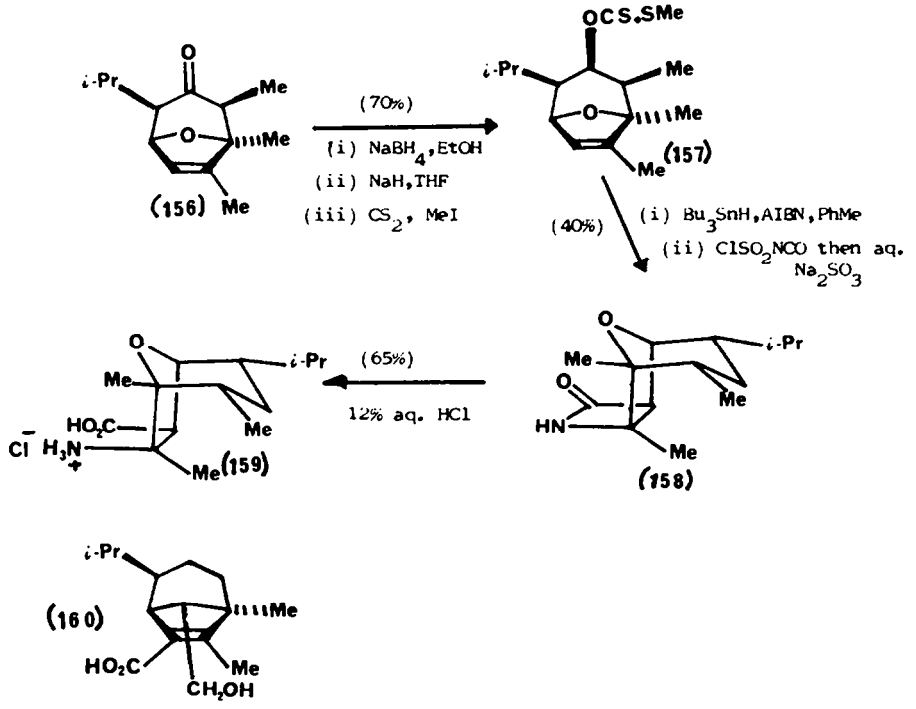
subsequent reduction and hydrolysis of the β-lactam (**158**) provided the amino acid (**159**), a proposed precursor for analogues of the plant growth-promoting agent helminthosporic acid (**160**)[82] (Scheme 51).

Finally, there are a few examples of intramolecular reactions between oxyallyl cations and furans, and the one reported by Noyori *et al.*[83] is shown in Scheme 52. Cycloadduct **161** has the basic skeleton of a number of sesquiterpenes, e.g. ambrosic acid (**162**) and daucol (**163**). Similar experiments were carried out by Föhlisch and Herter,[84] and these are also shown in Scheme 52.

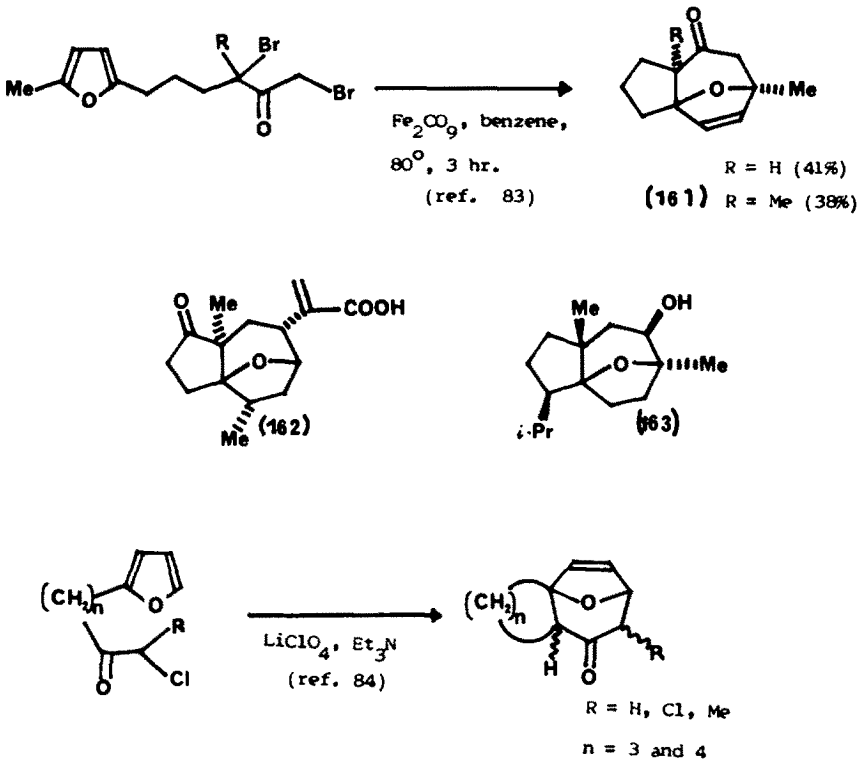
The equivalent reaction with substituted cyclopentadienes is also of interest (Scheme 53), but has yet to be accomplished, though Hoffmann *et al.* have carried out a related cycloaddition that involved an allyl cation rather than an oxyallyl cation (Scheme 54) and produced 9,10-dehydro-2-norzizaenes (**164**).[85]

3.5. *Reactions with thiophenes*

Several attempts have been made to obtain cycloadducts with thiophenes, but in each instance[3,86] substitution products were obtained (Scheme 55).

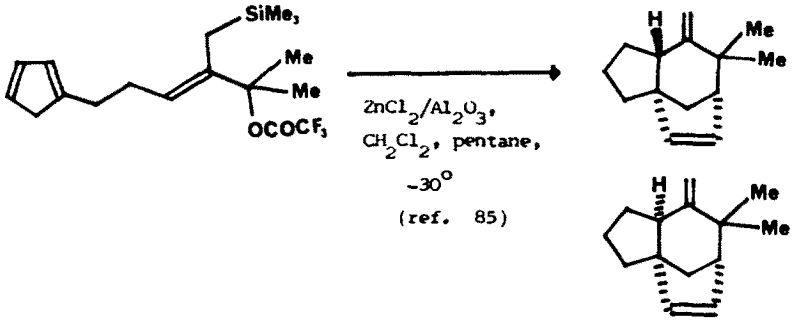


Scheme 51.



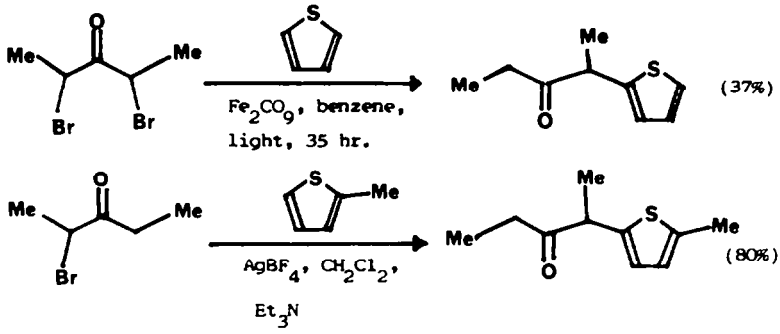
Scheme 52.

Scheme 53.



(164) Yield: ca. 8% of each isomer

Scheme 54.



Scheme 55.

3.6. *Reactions with alkenes*

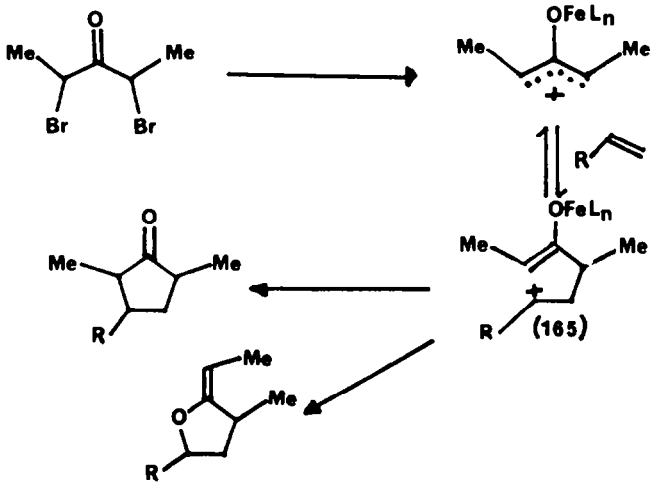
Concerted cycloadditions between oxyallyl cations and olefins are, of course, symmetry forbidden, but a non-synchronous process is possible provided that the intermediate cation, e.g. **165**, has sufficient stability. A careful choice of cation-stabilizing group is thus crucial (Scheme 56).

Noyori and co-workers have carried out a large number of cycloadditions with aryl-substituted alkenes,[87] and representative examples are given in Scheme 57. Fair to good yields of substituted cyclopentanones were obtained on up to the 40 mmol scale, though alternative products predominated when tertiary dibromoketones were employed.

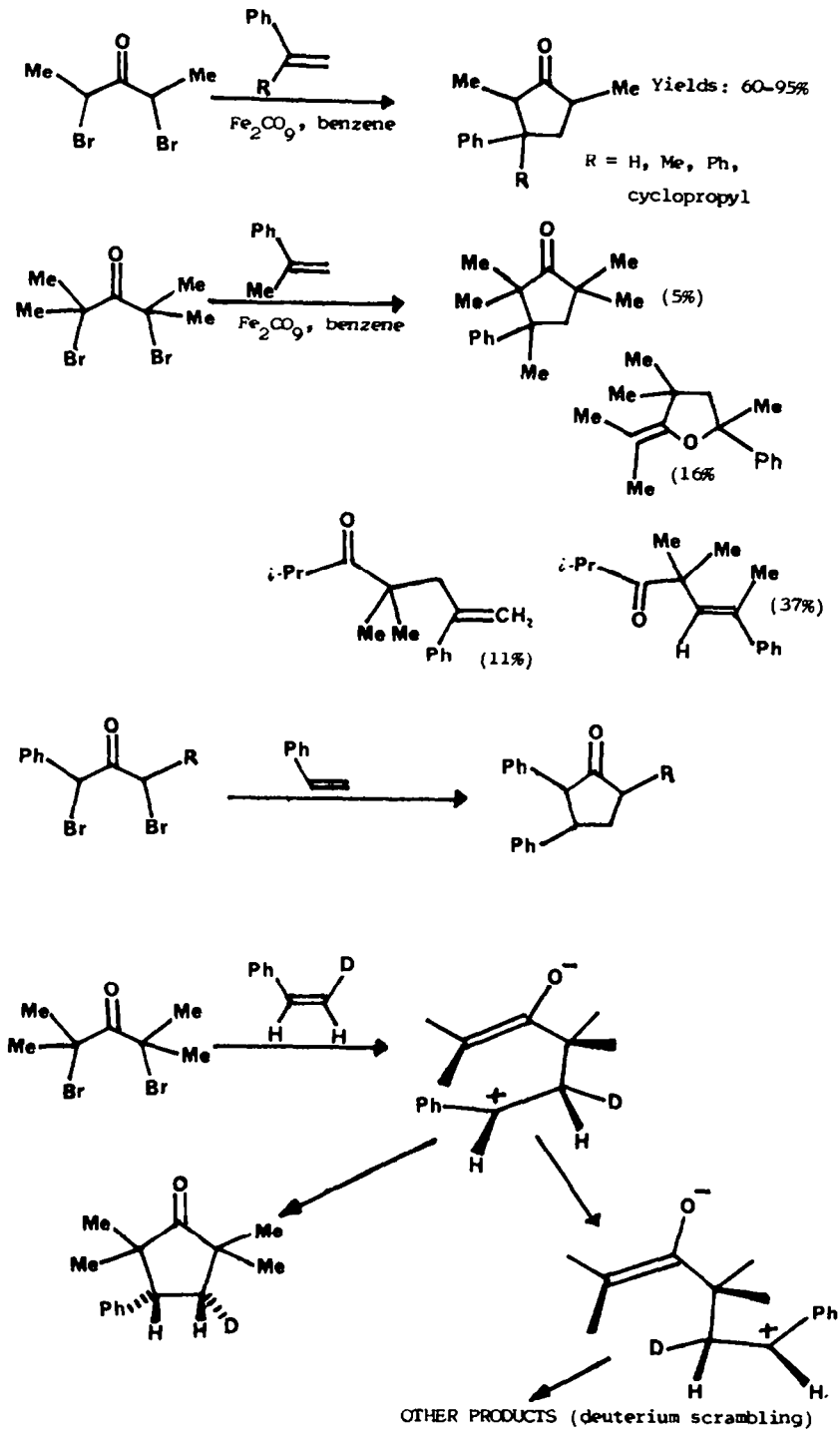
Several features are worthy of note. The olefin participates in the cycloaddition in a stereospecific fashion with overall retention of configuration, but acyclic products are produced in a non-stereospecific fashion, probably because the favoured intermediate cation can adopt a variety of conformations before hydrogen (or deuterium) is lost (Scheme 57). Regioselectivity is observed, and can be explained through a consideration of the relative stabilities of the intermediate zwitterions (**165**). Finally, from a practical point of view, only diiron enneacarbonyl can be used with any degree of success, and zinc–copper couples in benzene or dimethoxyethane do not produce cyclopentanones.

One natural product, the sesquiterpene α-cuparenone (**166**), has been synthesised using this methodology (Scheme 58),[88] and high regioselectivity was a notable feature of the synthesis.

Several cycloadditions have been carried out with alkyl-substituted olefins, and the intramolecular reaction shown in Scheme 59 provides a cogent example of the ease with which a complex natural product—campherenone (**167**)—may be assembled using oxyallyl techniques.[83] The full potential of intramolecular cycloadditions between oxyallyl cations and alkenes has yet to be realized.



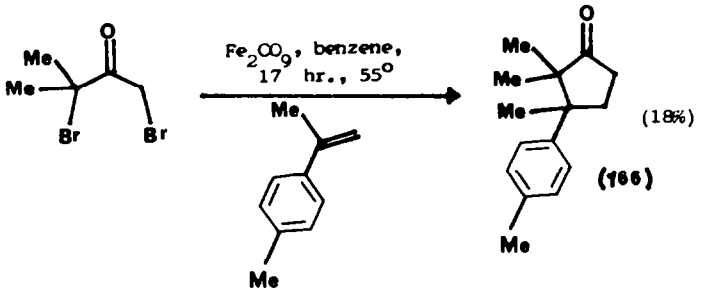
Scheme 56.



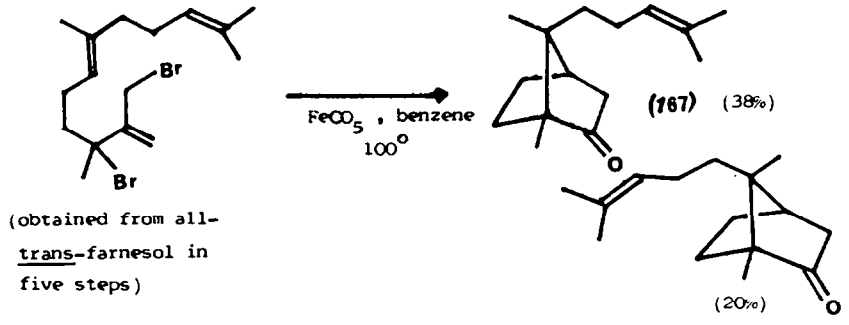
Scheme 57.

Enamines also afford the possibility for stabilization of intermediate cations like **165**, and Noyori and co-workers have carried out a large number of reactions[89] of the type exemplified in Scheme 60. Once again only diiron enneacarbonyl in benzene produced good yields of products, though zinc–copper couples in dimethoxyethane do provide products, but in poor yield.

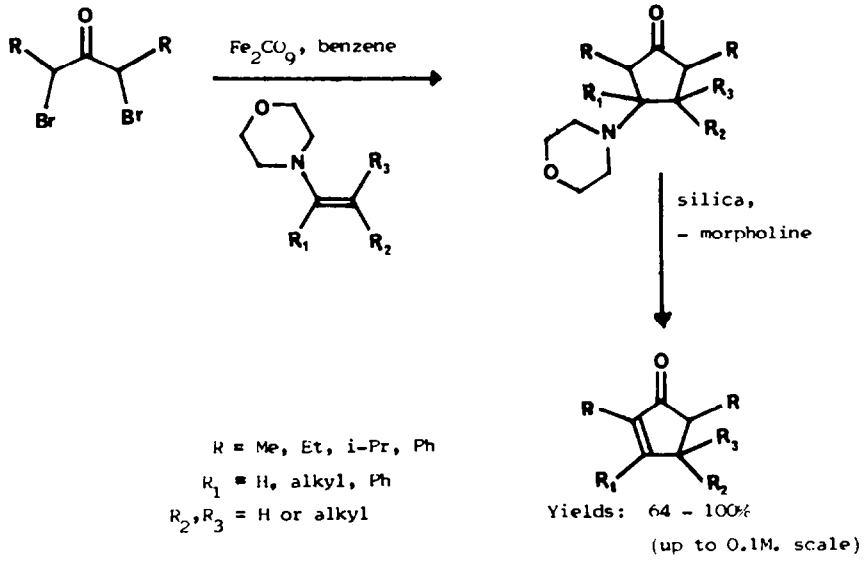
Noyori carried out the very interesting experiment shown in Scheme 61, in which a mixture of furan and enamine was used. This suggested that both 3+2 and 3+4 cyclocoupling reactions were proceeding via a common iron oxyallyl intermediate (**168**).



Scheme 58.



Scheme 59.

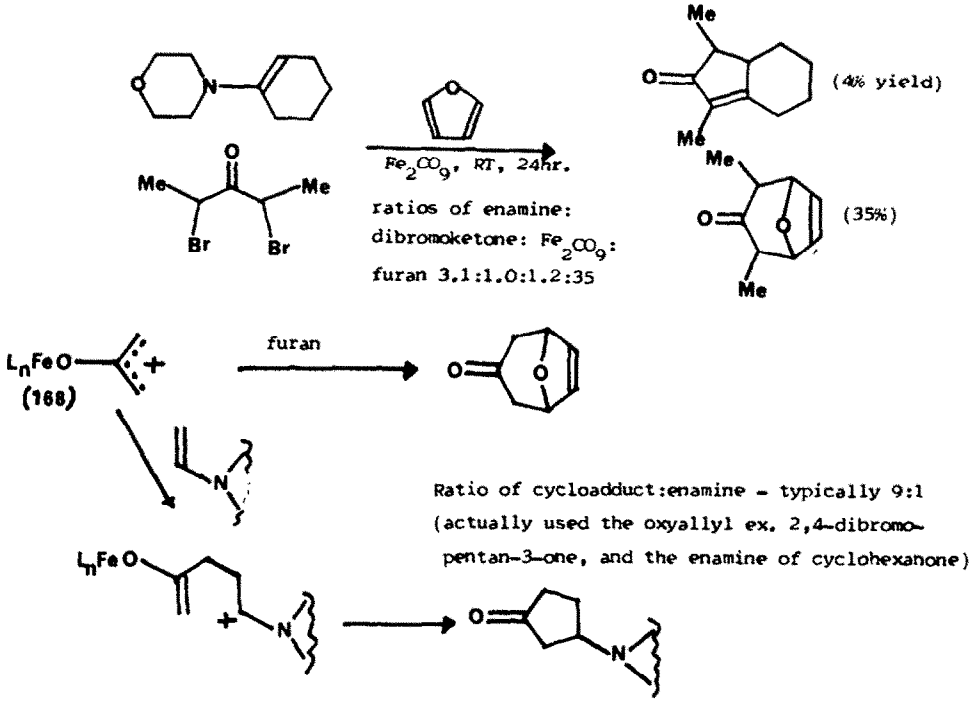


Scheme 60.

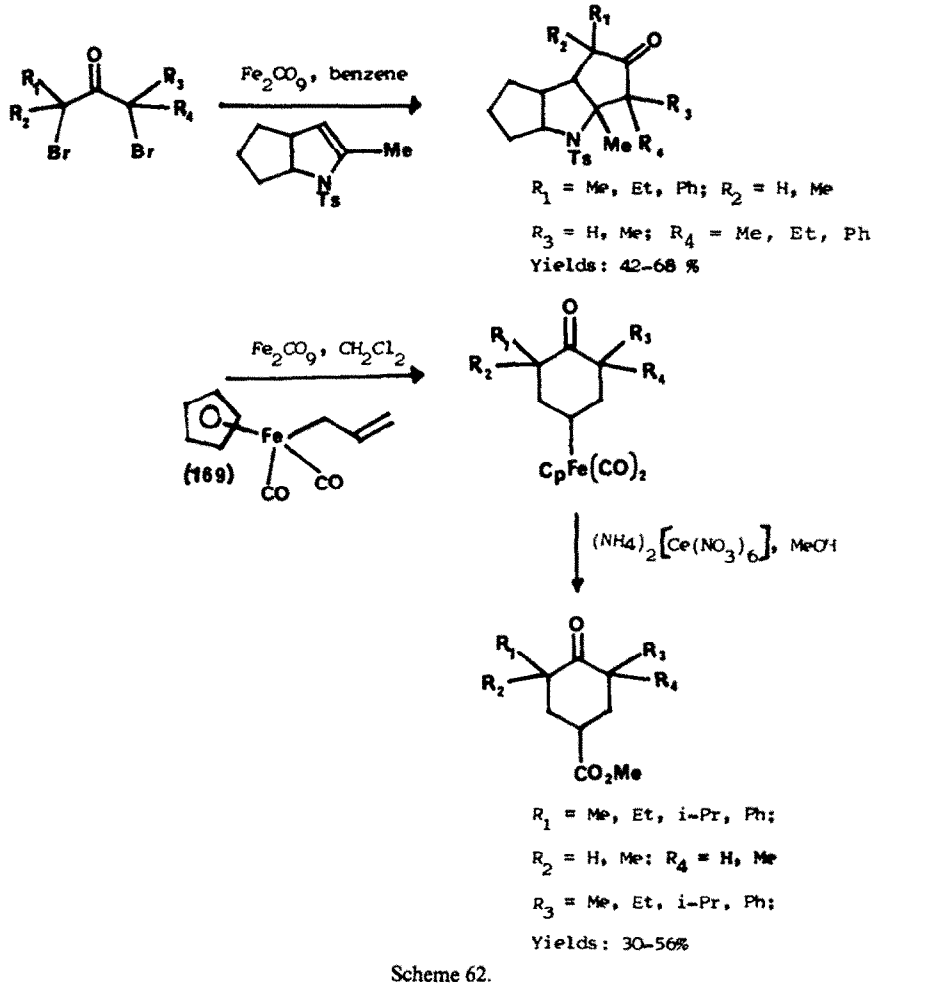
More recently, Hegedus and Holden have used tosyl enamines as olefinic components of cycloadditions with oxyallyls, and also the η^1-allyl(cyclopentadienyl)iron dicarbonyl (**169**) for the construction of substituted cyclohexanones (Scheme 62).[90]

The synthetic utility of these reactions has not been exploited, except that Noyori and co-workers have shown[89] that dialkylazulenes, e.g. **170**, are readily accessible via the sequence shown in Scheme 63.

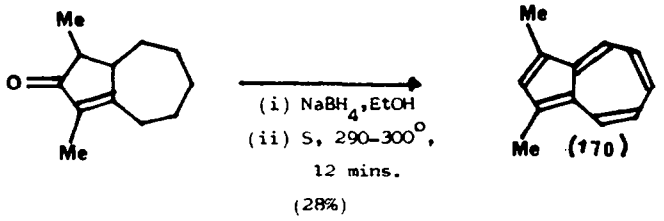
The main disadvantage of all of this chemistry is that tetrabromoacetone will not participate in these reactions to yield cycloadducts, with the result that all of the products carry (unwanted) alkyl or aryl substituents.



Scheme 61.



Scheme 62.



Scheme 63.

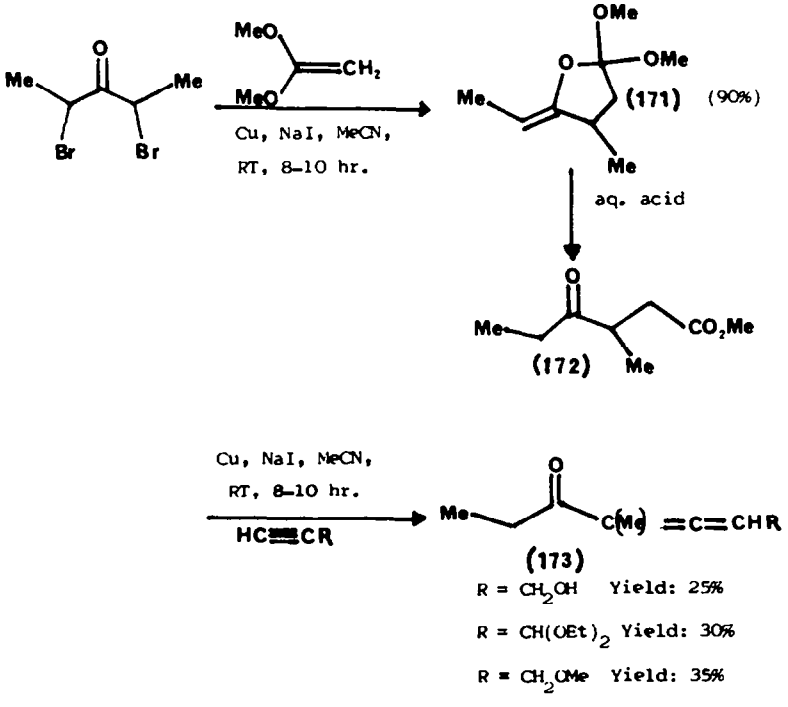
Finally, Cowling and Mann attempted to add the electron-rich alkene dimethoxyethene to the oxyallyl from 2,4-dibromopentan-3-one, in the hope of preparing a cyclopentane-1,3-dione; but obtained instead orthoester **171**.[91] This could be easily converted into ketoester **172**. Attempted cycloadditions with terminal acetylenes produced only the keto-allenes (**173**),[91] and both types of reactions are illustrated in Scheme 64.

3.7. *Reactions with solvents*

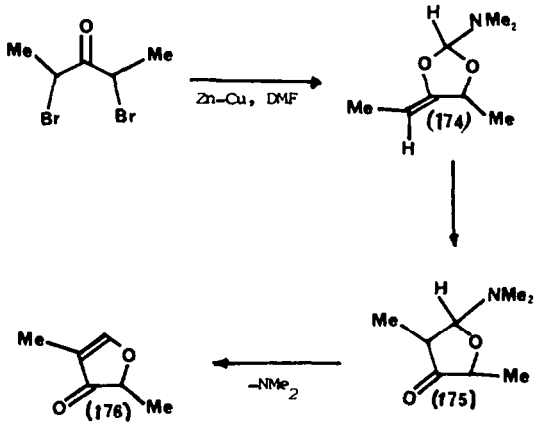
Some of Hoffmann *et al.*'s original reports[92] concerned the reactions of α,α′-dihaloketones with a zinc–copper couple in the presence of dimethyl formamide (DMF), with obtention of 4-alkylidene-2-dimethylamino-1,3-dioxolanes, e.g. **174** (Scheme 65). This work provided some of the earliest evidence in favour of the intermediacy of oxyallyl cations. The dioxolanes are very sensitive to heat, moisture, light and oxygen, and had to be isolated by extraction of the reaction mixture with pentane at −40 to −50°. On standing they spontaneously rearrange to yield 5-dimethylamino-tetrahydrofuran-3-ones, e.g. **175**, and these then lose dimethylamine to produce 3(2H)-furanones, e.g. **176** (Scheme 65).

Noyori *et al.* have prepared the muscarine analogue (**177**) from furanone (**176**) using this methodology[93] (Scheme 66).

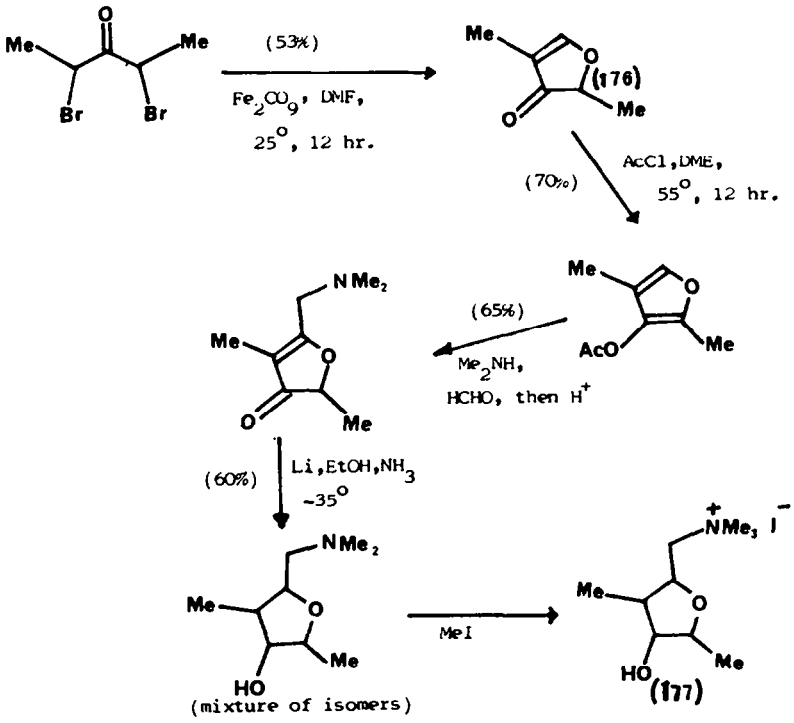
A related cycloaddition reaction occurs with acetonitrile, and these cycloadducts (**178**) are usually isolated in varying amounts when the Cu/NaI method is employed since this uses acetonitrile as solvent[3,94] (Scheme 67).



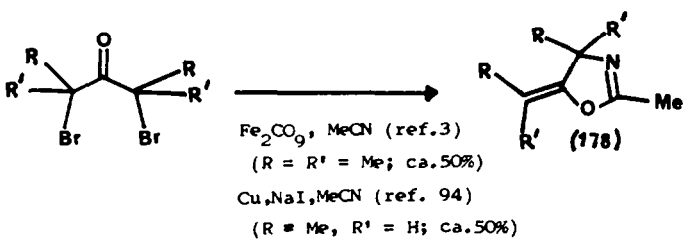
Scheme 64.



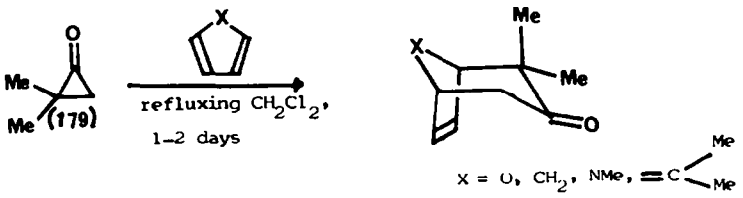
Scheme 65.



Scheme 66.



Scheme 67.



Scheme 68.

4. MISCELLANEOUS CHEMISTRY

4.1. *Oxyallyl cations from cyclopropanones and allene oxides*

As mentioned previously, cyclopropanones and allene oxides are formally in equilibrium with oxyallyl cations. Neither species is amenable to large-scale synthesis, and little work has been carried out with them, but two examples are of interest, and are shown in Schemes 68 and 69.

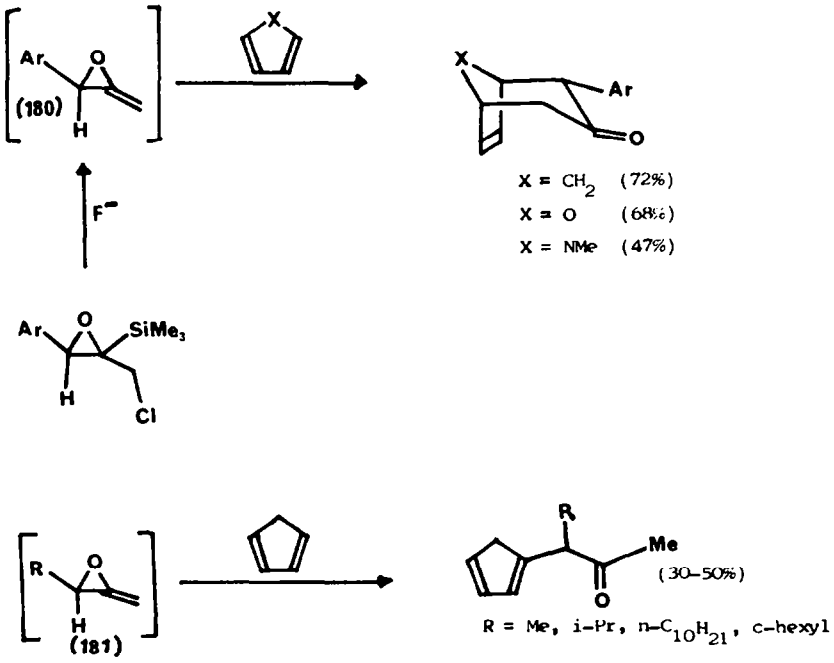
Turro *et al.* showed that 2,2-dimethylcyclopropanone (**179**) reacted efficiently with furan, cyclopentadiene, N-methylpyrrole, and dimethylfulvene to yield the anticipated cycloadducts (Scheme 68),[95] but no cycloaddition occurred with butadiene or with anthracene.

Chan and Ong employed a variety of allene oxides in attempted cycloadditions with cyclic dienes, but only aryl substituted species (**180**) yielded the desired products. Alkyl substituted allene oxides (**181**) produced substituted cyclopentadienes when the parent diene was used (Scheme 69).[96]

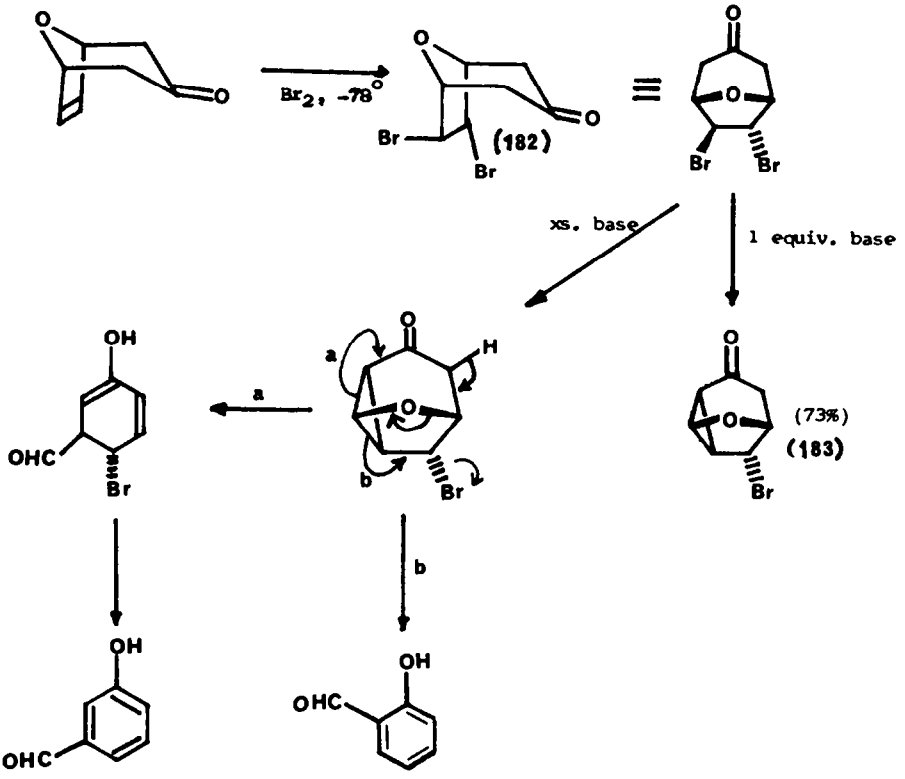
4.2. *Rearrangements of oxabicyclo*[3.2.1]*octanones*

Although not entirely within the scope of this review, a number of rearrangement reactions of 8-oxabicyclo[3.2.1]octanones are worth mentioning. The substrates for these reactions are derived from cycloadducts that have been mentioned in earlier sections. Sampath and Schore treated dibromide **182** with base, and observed the formation of both *o*- and *m*-hydroxybenzaldehydes. Under carefully controlled conditions they were able to isolate and characterize intermediate **183**, and proposed the mechanism shown in Scheme 70.[97]

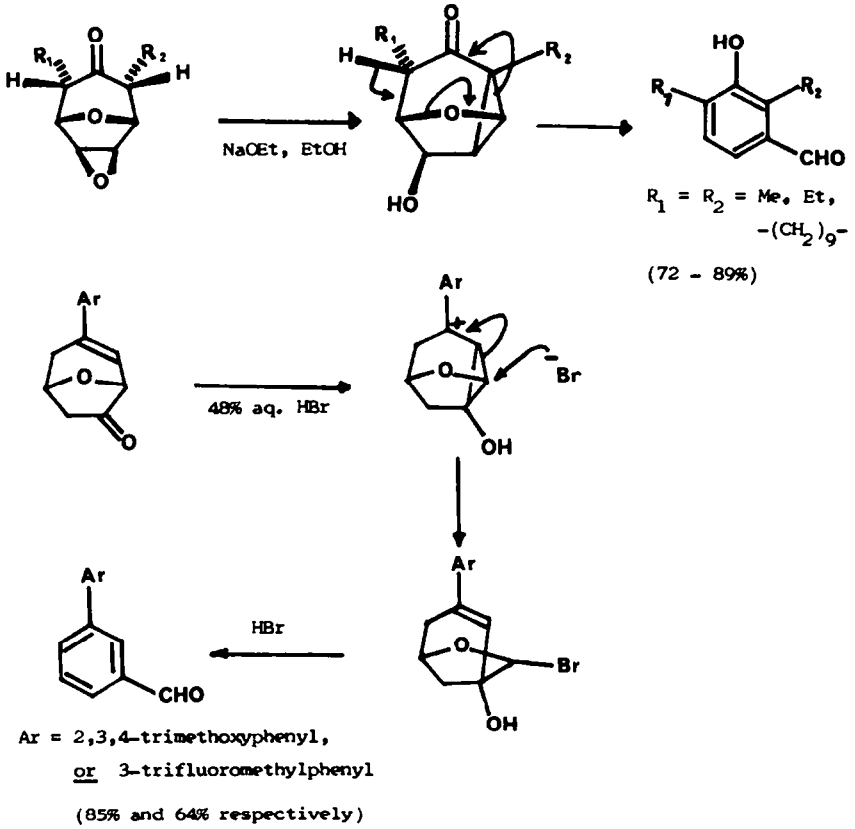
Two related reactions have been carried out more recently by Föhlisch and Herrscher,[98] and by Mann *et al.*[24] and in each case *m*-substituted benzaldehydes were the major products. These rearrangements, and respective postulated intermediates are shown in Scheme 71.



Scheme 69.



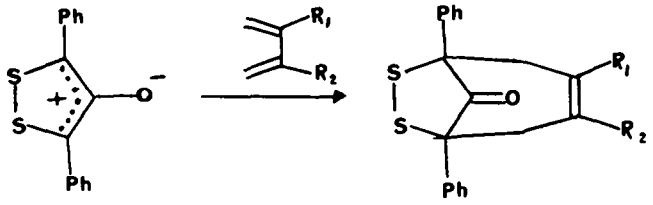
Scheme 70.



Scheme 71.

4.3. *Cycloadditions of mesoionic* 1,2-*dithiol*-4-*ones*

A reaction described by Hanke and Gotthardt[99] provides an interesting example of a type B mesoionic system[100] behaving as an oxyallyl cation towards acyclic dienes (Scheme 72). The synthetic utility of this process has not been explored.



5. CONCLUSION

Oxyallyl cations have been used in synthesis for at least 15 years, and the scope of their intermolecular cycloaddition reactions with dienes and alkenes have been amply demonstrated. The intramolecular versions of these reactions have scarcely been considered, and this could provide a fertile area for future study. In addition, the demonstration[54] that alkylation of easily accessible 8-oxabicyclo[3.2.1]oct-6-ene-3-ones can be achieved via their enol silyl ethers (Scheme 49), obviates the necessity of using complex haloketones. This allows access to complex oxabicycles by the use of commercially available tetrachloroacetone and simple furans, and since a number of methods are now available for the controlled cleavage of such oxabicycles, a wide variety of natural products and analogues should now be more easily accessible.

Addendum—A number of papers concerning the use of oxyallyl cations have appeared since completion of this report. These include the synthesis of 11-oxatricyclo[5.3.1.$0^{2,6}$]undecane derivatives via octacarbonyl dicobalt-catalysed cyclization of alkynes and 8-oxabicyclo[3.2.1]oct-6-enes (produced using oxyallyl methodology);[101] the use of zinc in conjunction with ultrasound for the generation of oxyallyls from α,α′-dibromoketones;[102] and the generation of cyclopropanone/oxyallyl cation intermediates from α-mesyloxyketones.[103]

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